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Review Article

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Ovarian Cancer Recurrence. A Review

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Abstract

Ovarian cancer is the first cause of death among gynecological malignancies with a high incidence of relapse in the first 3 years after initial operation.

The 3 most common cause of relapse is the chemoresistance of the tumor, the biological behavior of the tumor and the third is the inappropriate surgical excision.

Over the last years one of the most intriguing method in different cancer centers is the CRS+HIPEC.

We present herein the different option concerning the role of this procedure. We declares the 2 different options of relapse disease as ''residual'' which means not complete surgical procedure in the initial operation, and real ''recurrent'' disease.

The improvement in overall survival was maintained significant in HIPEC groups when compared to protocols without HIPEC.

In conclusion Hipec seems to be beneficial to prolong survival in patients with relapse disease.

Keywords: *Hyperthermic intraperitoneal chemotherapy (HIPEC), epithelial ovarian cancer (EOC), Cytoreduction (CRS).*

Introduction

Ovarian cancer is the first cause of death among gynecological malignancies (1). The surgical treatment represents the first option with the aim to achieve the optimal debulikng, followed by systemic chemotherapy (2). However, even achieving complete cytoreduction the majority of patients at stage III-IV develops a recurrence in a few years (3). To date, different treatment options are suitable to prolong the survival rate of these patients as monoclonal antibodies and targeted therapies as bevacizumab or PARP inhibitors, and biological therapy. However, the results obtained are still partial and not completely effective (4). One of the most attractive methods, currently available in several oncologic centers is the hyperthermic intraperitoneal chemotherapy (HIPEC). It is an effective method to deliver antiblastic drugs directly in the abdomen at the time of surgery, moreover the hyperthermia addiction allowed to enhance the tissue absorption, that is different depending on different factors as drugs administered and temperature reached, and consequently the cytotoxic action of chemotherapeutic drugs that reach the maximum effect between 40

and 43 centigrade (5). HIPEC treatment is adopted in different kind of cancer as gastric, colorectal and primary peritoneal carcinosis. For ovarian cancer treatment, this technique, was for a long time debated, however after the results of a randomized trial by van Driel et al. (6) HIPEC was inserted in NCCN guidelines as an optional treatment for interval debulking surgery (NCCN clinical practice guidelines Version 1.2019-March 8, 2019 OV-2).

Hipec in relapse disease

Relapse ovarian cancer remains a difficult problem in the management of epithelial ovarian cancer (EOC) with the recurrences rates arises to 50-70% 3 years after initial treatment. Among other factors as biology of primary tumor and chemo sensitivity the completeness of primary/interval surgery is also affecting the patient risk of ''relapse'' (7). A study from our team demonstrates the incidence of residual disease in 70% of cases (8).

By definition in this study the main sites of residual disease are if we observed deposits in remain great omentum, liver round ligament gallbladder and vaginal stump and recurrent disease included sural bowel mesenterium, pelvic floor and diaphragm (9). The most important finding is survival rates between residual and recurrent disease is the median overall survival in residual disease after CRS+HIPEC was 38m versus 26m in recurrent disease (8).

Hipec in recurrent disease

The use of Hipec for the secondary management of relapse due to advanced EOC has been more extensively investigated. The majority of trials are retrospective small case-control studies evaluating a small number of patients.

Recurrent Ovarian Cancer

Five studies accounting for 285 women evaluated the PFS differences among HIPEC and no-HIPEC administration in ROC (10,11,12). The general characteristics of ROC patients are described in Table 1. The HIPEC protocol characteristics of ROC patients are described in Tables 2 and 3.

Table 1. Recurrent ovarian cancer has general characteristics.

Author	Country	Year	Recruitment Period	EOC Stage (FIGO)	HIPEC Group, No. (%)	Control Group, No. (%)
Spiliotis (10)						
Platinum sensitive disease	Greece	2014	2006–2013	IIIC–IV	38 (51%)	36 (49%)
Platinum resistant disease	Greece	2014	2006–2013	IIIC–IV	22 (47.8%)	24 (52.2%)
Cascales Campos (13)	Spain	2015	2001–2012	I–IV	32 (59%)	22 (41%)
Baiocchi (12)	Brazil	2016	2000–2014	I–IV	29 (36.7%)	50 (63.3%)
Zivanovic (11)	Germany	2021	2014–2019	I–IV	49 (50%)	49 (50%)

Table 2. Recurrent ovarian cancer HIPEC protocol.

Author	Year	HIPEC Protocol			Type of Tumor: Serous, No. (%)		Type of Tumor: Others No. (%)	
		HIPEC Drug	Temp (°C)	Duration (min)	HIPEC	Controls	HIPEC	Controls
Spiliotis (10)								
Platinum sensitive disease	2014	Cisplatin 100 mg/m^2 + paclitaxel 175 mg/m^2	42.5	60	NR	NR	NR	NR
Platinum resistant disease	2014	Doxorubicin 35 mg/m^2 + paclitaxel 175 mg/m^2	42.5	60	NR	NR	NR	NR
Cascales Campos (13)	2015	Paclitaxel 60 mg/m^2	42	NR	NR	NR	NR	NR
Baiocchi (12)	2016	Mitomycin C 10 mg/m^2—Cisplatin 50 mg/m^2—Doxorubicin	41–42	90	18/29 (62%)	38/50 (76%)	11/29 (38%)	12/50 (24%)
Zivanovic (11)	2021	Carboplatin 800 mg/m^2	41–43	90	47/49 (96%)	NR	48/49 (98%)	NR

NR: not reported.

Pooled MD did not show a PFS significant difference between intervention and controls [MD 2.68 months

(95% CI −4.33 to 9.70 months); I2 = 95%].

Meanwhile, OS was reported in 2 trials (218 women) (10,11). Of those, Spiliotis et al. (10) reported data separately according to platinum resistance and sensitivity (10). Overall, pooled results did not report a significant difference between the two approaches in terms of OS (MD 6.69 months [95% CI −9.09 to 22.47 months]; I2 = 98%).

Table 3. Recurrent ovarian cancer BRCA mutation.

Author	**Year**	**No. (%) No BRCA Mutations (HIPEC-No HIPEC)**	**No. (%) BRCA Mutations (HIPEC-No HIPEC)**
Cascales Campos (14)	2014	NR	NR
Spiliotis (10)	2015	NR	NR
Platinum sensitive disease	2014	NR	NR
Platinum resistant disease	2014	NR	NR
Cascales Campos (13)	2015	NR	NR
Baiocchi (12)	2016	NR	NR
Zivanovic (11)	2021	39/49 (80%)–38/49 (78%)	10/49 (20%)–11/49 (22%)

NR: not reported.

A phase I trial from Zivanovic et al. evaluated the dose of cisplatin (maximum tolerated) for HIPEC and a phase II trial is currently under investigation (15).

Another paper from France in recurrent chemosensitive and chemoresistant EOC patients demonstrates improves of survival in lower PCI <8 and CC0 score. The results also demonstrate not significant difference between platinum sensitive or resistant tumors (16). The last observation demands and need more available data (17).

A Spain study evaluates the role of HIPEC in primary and secondary recurrent disease from EOC and demonstrates an improvement of OS in both groups and also in both CC0 and CC1 cytoreduction groups

(18). The main question concerning the role of HIPEC in this study is that the survival is similar with other studies without HIPEC but treated with secondary cytoreduction only (19,20).

Cascales-Campos et al. (21) in 2015 evaluate the CRS solely versus CRS plus HIPEC in platinum-sensitive EOC. The results demonstrate same PFS (22 vs. 21 m) in favor of CRS alone. The only explication for this result is that in the 39 patients of HIPEC group the mean PCI score is significantly higher. Some investigators suggest also a bias in the choice of paxcitaxel as HIPEC regimen which it may not be effective for use (21).

Fagotti et al. (22) in a case control study with 3 arms CRS + IV chemo, (13 pts) IV chemotherapy alone (24 pts) and CRS + HIPEC (30 pts). The results demonstrate similar RFS and only a minimal pattern of recurrence with HIPEC group to achieve a longer secondary PFS after initial treatment (22).

The first RTC in the field was published by Spiliotis et al. (23) evaluated the role of HIPEC at first recurrence and was highly criticized due to methodological issue.

The authors included 120 patients with advanced stage EOC (> IIIc) who had disease recurrence and were randomized to either receive CRS plus HIPEC followed by systemic chemotherapy or CRS with systemic chemotherapy alone.

Another question is what the role of systemic chemotherapy in relapse disease is.

There is some evidence that the use of second line systemic chemotherapy in relapse ovarian cancer before the CRS + HIPEC may offers a survival benefit in PFS and OS as compare with CRS + HIPEC alone (46 versus 31 m P=0.013) (24).

The main debate especially in multidisciplinary tumor conferences is what kind of IP chemotherapy would be recommended for a woman if she was diagnosed with advanced ovarian cancer. There are two attitudes: one with norm thermic IP based on the results of GOG172 with a median global survival of 65.2 m but with possibilities of successfully finish the treatment schedule very low 42%. On the other hand, the choice of HIPEC which with acceptable morbidity and mortality rates with acceptable risk the 5 years survival rates higher that 60% (25). The fact that although GOG 172 showed worse toxicity in the ip group, the most recent GOG 252 study demonstrated that the overall rates of toxicities and discontinuation among iv and ip chemotherapy arms were comparable (26).

An article from Fotopoulou et al. (27) arise the question concerning HIPEC: is a hope of hype in the fight against advanced ovarian cancer? The response from the authors of this article is that: Publicly available

evidence addressing the value of HIPEC in EOC is rather inconclusive, revealing contradictory and inconsistent results while some studies even report harm to the patients from a higher morbidity. On this ground we cannot recommend the implementation and use of HIPEC outside of a randomized clinical trial setting (27).

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