A review analysis of cytoreductive surgery and HIPEC in gynecological cancers

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Abstract

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a procedure to delivered chemotherapy directly while heating in the peritoneal cavity after a special surgical effort which described as cytoreductive surgery (CRS).

The aim of this method is to eliminate surgically and medically all the visible tumor deposits from different tumors.

The last decade the interest of this treatment in peritoneal metastasis of different gynecological tumors as ovarian, endometrial or cervical are reported with different trials.

This article reviews the current literature and evidence of this procedure.

Keywords: Cytoreductive Surgery (CRS); Hyperthermic Intraperitoneal Chemotherapy (HIPEC); Gynecological Cancer, Epithelial ovarian cancer (EOC)

1. Introduction

Epithelial ovarian cancer (EOC) is the most lethal type of gynecological cancer and accounts for approximately 50% of the related deaths. Serous adenocarcinoma is the most common histological subtype. Approximately 90% of the patients are diagnosed with the disease spread outside the ovaries (Stage II-IV) with a poor prognosis. In advanced stage EOC, tumor spreads from the lower pelvis to the upper abdomen by invading the peritoneal surfaces. Majority of advanced stage EOC patients die within three years.

On the other hand, endometrial cancer is the most common gynecological cancer in the developed countries. The most common histopathological type in endometrial cancer is the endometrioid subtype, followed by the serous subtype. Although serous endometrial cancer is the histological type which constitutes approximately 10% of endometrial cancer, it has the worst prognosis, similar to those with serous histology of ovarian origin. Furthermore, two-thirds of the patients with serous histological subtype have a cancer spread outside the uterus at the time of diagnosis. Finally the third gynecological cancer is cervical cancer which affects young women.

2. Management

The standard treatment approach in both EOC and endometrial cancer patients with serous histology is the surgical removal of all visible lesions in the abdominopelvic cavity followed by the administration of systemic chemotherapy. The term is “Cytoreductive Surgery” (CRS). It aims to remove organs and peritoneal surfaces infiltrated with tumoral...
tissue without leaving any visible lesions in the abdominopelvic cavity. Thus, via systemic platinum-based chemotherapy, it is aimed to achieve the microscopic cytoreduction of the remaining tumor. However, 80% of women with advanced disease EOC will recur despite the appropriate treatment approach mentioned above.

Platinum resistance in EOC is a well-defined clinical entity with worse survival defined as the development of relapse within the first six months after the end of systemic platinum-based chemotherapy. Overall survival (OS) in the presence of platinum-resistant disease is approximately 12 months, and progression-free survival (PFS) is three months. In the case of recurrence after first-line therapy, response to platinum is seen in less than 10% of platinum-resistant patients and second-line chemotherapeutic agents are preferred.

Therapeutic strategies including targeted agents such as bevacizumab, olaparib, cediranib, immunotherapeutic agents such as atesolizumab, and hyperthermic procedures have drawn attention.

Cervical carcinoma is the fourth most common cancer among women worldwide. The predominant histological type is squamous cell carcinoma meanwhile adenocarcinoma and adenosquamous cell carcinoma represents 10-15%. Other or unspecified histology represent the remaining 10-15%.

Typical metastatic or recurrent sites are the pelvis and lymph nodes, but peritoneal metastasis have also been described with a very low prevalence, about 5%. A large population study in Netherlands confirmed that 1% of the patients with cervical cancer, presented with peritoneal metastasis. The mean age at diagnosis of only advanced stage patients was 51.4 years. Thirty-eight percent had an adenocarcinoma and 44% had a squamous cell carcinoma. Fifth-five percent of patients had PM without other distant metastases.

Endometrial cancer is the most common malignancy of the female genital tract. For the cancers detected at an advanced stage or peritoneal relapse the prognosis is poor.

3. The role of HIPEC

The last years the role of cytoreductive surgery and HIPEC are evaluated.

EOC is the leading cause of death in women with gynecological cancers, and the annual mortality rate rangers from three to nine per 100.000 women. In many cases with widespread peritoneal disease, searches have been sought for alternative ways to increase the effectiveness of chemotherapy because of the development of intraperitoneal recurrence despite complete CRS and adjuvant chemotherapy.

The administration of chemotherapy directly into the abdominal cavity provides a higher drug concentration on the peritoneal surface, thereby enhancing the cytotoxic effect of chemotherapy.

Moreover, hyperthermia itself has been described to boost the effect of chemotherapy with a direct cytotoxic effect on tumor cells. The philosophy of HIPEC is based on these two basic ideas. Since chemotherapeutics have a tissue penetration depth of one to two mm, it is accepted that cases without residual macroscopic tumor at the end of cytoreductive surgery will be more likely to benefit from this strategy. In ovarian cancer HIPEC may be administrated in many different time periods; e.g. at the time of primary staging surgery, after the primary surgery + completion of adjuvant chemotherapy as consolidation therapy, at the time of interval cytoreductive surgery performed after neoadjuvant chemotherapy, as salvage therapy or at the time of secondary/tertiary CRS. The most preferred period of HIPEC administration is during CRS for recurrent disease. In addition, administration of HIPEC at the time of interval cytoreductive surgery has recently come to the fore.

There are a limited number of randomized prospective studies on HIPEC in gynecological cancers. In a multicenter prospective observational study performed between 2007 and 2013, patients (n=54) who had undergone surgery + HIPEC at various periods (during primary staging surgery, interval cytoreductive surgery, and secondary CRS for recurrent disease) were evaluated by Coccolini et al. Grade 3 and 4 complications were reported in 35% and grade 5 complication in 6% (n=3) of patients. In a recent meta-analysis of 37 studies conducted by Huo et al. grade 3 and 4 morbidity rates after CRS+HIPEC in patients with recurrent.
The first randomized prospective study on HIPEC in gynecological cancers was published in 2015 by Spiliotis et al. In this study, women advanced stage EOC (n=120) were randomized in an eight-year period between 2006 and 2013, after primary staging surgery + adjuvant systemic chemotherapy.

3.1. Patients divided into two groups

CRS + adjuvant chemotherapy was applied to group A and CRS + HIPEC + adjuvant chemotherapy to group B. When the results were analyzed, the mean survival in group B was found to be significantly increased compared to group A. (26.7 vs 13.4 months, p<0.006). In addition, when the patients in group B were subdivided into platinum-resistant and platinum-sensitive disease groups, survival had no statistical difference between the groups (26.6 vs. 26.8 months). The study also revealed that complete cytoreduction was associated with longer survival in parallel with many other studies. The main criticisms have focused on the selection of primary and secondary targets, lack of PFS data, methodological and scientific errors in statistical analysis and randomization, as well as the absence of postoperative complication data. Recently, a prospective study has been published by van Driel et al. Patients with advanced stage ovarian cancer (n=245) were divided into two groups after receiving neoadjuvant chemotherapy. The first group of the patients (n=123) were treated with CRS + adjuvant chemotherapy and the second group (n=122) with CRS + HIPEC + adjuvant chemotherapy. When the results were evaluated, PFS in the first group was 10.7 months and in the second group it was 14.2 months (p=0.003). Moreover, OS was 33.9 and 45.7 months, respectively (p=0.01). In addition, the rates of severe morbidity in both groups (25% vs 27%, respectively) were similar. This study has been the subject of many criticisms. Many authors stated that methodological errors were made in the selection of the study plan (e.g. the institution giving the most patients to the study, having the least effect on the results) and serious postoperative complications were also neglected. For cervical, a retrospective analysis from our center in 30 patients, with peritoneal metastasis demonstrate a survival benefit of the overall survival in CRS+HIPEC group versus CRS alone (38±4,8m vs 12.00±1,5 m).

In endometrial cancer peritoneal metastasis better PFS rates after CRS plus HIPEC were observed with a 5 year survival rate of 23%.

On the other hand, recently a multi-institution study from PSOGI and BIG RENAPE groups were not observed any statistical significance in survival analysis. The major bias of this study is that, in "CRS+HIPEC” group, 96,7% of women were treated for recurrence while in "CRS only” 83,3% were treated for primary disease.

In a study from Italy and Greece for selected patients with peritoneal metastasis from endometrial cancer indicated a 5 year survival rate of 30% in the CRS and HIPEC group.

4. Conclusion

In conclusion, hyperthermic intraperitoneal chemotherapy (HIPEC) is a method administering anticancer agents directly while heating the abdominal cavity.

In many observational studies and some randomized phase III trials there is a growing evidence of the efficacy of CRS plus HIPEC in gynecological cancers, and could be one of the new therapeutic strategies for such disseminated peritoneal lesions.

On the other hand, since the usage regimen and temperature setting of HIPEC are not standardized it is necessary to consider more clinical trials for the optimization and establishment of HIPEC in the future.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.
References


