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Original Research Paper

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INTRAPERITONEAL ADMINISTRATION OF CHEMOTHERAPY IN ADVANCED STAGES OVARIAN CANCER

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ABSTRACT

INTRODUCTION: Ovarian cancer represents one of the major concerns in the everyday clinical practice as it known to be the most lethal gynecological malignancy with most of the patients being diagnosed at a late stage. The aim of this paper is to provide an up to date and discuss the recent available literature considering the use of intraperitoneal chemotherapy in advanced stages of ovarian cancer.

METHODS: The latest available literature in PubMed regarding the use of intraperitoneal administration of chemotherapy in advanced stages of ovarian cancer was searched, from 2017-2018 related articles.

RESULTS: Results of chemotherapy depend on the administration way. Studies support that intraperitoneal chemotherapy for advanced stages of ovarian cancer offers significant advantages, better prognosis while increases overall survival. Of great importance seems to be the intraoperative hyperthermic intraperitoneal chemotherapy that reaches much better results compared to current therapies.

CONCLUSIONS: Current routine therapies do not significantly improve the prognosis of patients, therefore novel therapeutic options are being explored to enhance the current treatment efficiency against ovarian cancer. Conventional intravenous administration of chemotherapy is proven to be one of the most effective therapeutic options, however, intraoperative hyperthermic intraperitoneal chemotherapy combined to cytoreductive surgery seems to achieve prosmising results in overall survival, however, further studies are needed to reach safe conclusions.

KEYWORDS : ovarian cancer, chemotherapy, cisplatin, carboplatin

INTRODUCTION

Epithelial ovarian cancer is known to be the most lethal gynecological malignancy with the epidemiology ranging from 30% to 90% (1). It represents the 13th most common cause of cancer deaths and the 10th most common cancer among women in the United States (2,3). Almost nine out of ten ovarian cancers have been classified as Epithelial Ovarian Cancers (OC) with patients diagnosed having a 47% 5-year-survival rate (4). The existing diagnostic tools mainly involve pelvic examination, serum cancer antigen 125 (CA125) measurements, Computed tomography (CT) scan, Magnetic resonance imaging (MRI) scan, Positron emission tomography (PET) scan and transvaginal ultrasound, and even though some of these tests are of high diagnostic value, unfortunately, most patients are diagnosed at a late-stage of the disease (5,6). Until now the standard therapeutic protocol for advanced s consists of initial surgery with macroscopically complete resection followed by platinum-based intravenous (IV) combination chemotherapy. Depending on several variables, at the time of recurrence, either further palliative chemotherapy or salvage surgical therapy may be selected (6).

The aim of this paper is to present and discuss the role of intraperitoneal (IP) administration of chemotherapeutic agents.

Chemoresistance in ovarian cancer

Although there is a growing understanding of ovarian cancer, early diagnosis still remains the most important prognostic factor. Several previous studies reported that non-coding RNAs have a key role in regulating various biological processes of OC, such as chemoresistance, affecting prognosis of the disease (7).

Chemoresistance, has been classified into intrinsic and acquired, and it is known to be a common phenomenon in chemotherapy. It has been observed that chemoresistance induces cancer growth acceleration and cancer progression-mortality. Intrinsic resistance exists in a population of chemo-naive patients, and causes the ineffectiveness of initial chemotherapy. On the opposite, acquired resistance emerges during treatment (8). Fortunately the introduction of new drugs and techniques (intraperitoneal administration of chemotherapy, taxanes, dose-dense regimens) combined to local therapies have improved survival. In addition, novel surgical techniques have resulted in less microscopic residual disease after cytoreduction, that also affects positively the overall survival (OS) rates (9). Based on the strategy followed for carcinomatosis of gastrointestinal origin, a combination of maximal cytoreductive surgery with intraoperative hyperthermic IP chemotherapy (HIPEC) has been proposed as a promising therapy for advanced OC with the rate of recurrence of peritoneal disease among patients treated with HIPEC reaching even 29% points lower than the rate among other therapeutic options (10).

Current and Future Perspectives of Intraperitoneal Chemotherapy Infusion

Relapses of ovarian cancer have poor prognosis and overall survival (OS) as they are directly related to the histological cell type, patient's performance status, size and number of the relapse. The most frequent sites of recurrence are liver, lung, pelvis, peritoneum, central nervous system and lymph nodes (11,12). To date, it is clear that chemotherapy has a key role on the main goal of surgery for ovarian cancer that is the complete cytoreduction to no gross residual disease. However, recent studies support that chemotherapy has different results depending on the administration way. Current data indicate that IP chemotherapy is superior to intravenous treatment alone and that combination of

cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have produced encouraging results with improved disease-free and overall survivals.

Shi et al., studied the efficacy of adding IP chemotherapy to standard first-line IV chemotherapy in epithelial ovarian cancer (EOC) patients. The authors observed that IP prior to IV chemotherapy produced an increased 12-month non-progression rate and a longer time to second subsequent anticancer therapy (TSST) than IP therapy with EOC. The authors also reported that long-term follow-up is warranted to identify the effects of IP therapy on overall survival (13).

In order to test the potential increased long-term survival, in selected groups of patients with peritoneal carcinosis (PC), Montori et al., analyzed the results of 150 patients (gastric cancer n=40, colon cancer n=31, appendiceal cancer n=18, ovarian cancer n=49, others n=12) who had previously undergone CRS and HIPEC as locoregional treatment. The authors concluded that the combination of CRS and HIPEC could achieve a better long-term survival with acceptable morbidity and mortality (14).

Additionally, in the studies by Ceresoli et al., and Coccolini et al., the oncologic results of CRS were compared to CRS/HIPEC combined therapy, in order to examine wether HIPEC prolonged disease-free survival (DFS) and OS in advanced primary ovarian cancer, while giving particular attention to the pattern of recurrence. Use of CRS combined to HIPEC with cisplatin-paclitaxel for advanced EOC is feasible with acceptable morbidity and mortality while HIPEC was also reported to affect the relapse pattern with lesser peritoneal recurrence and had a positive result considering OS (15,16).

Tempfer et al., presented a study where a phase I, single-arm, non-randomized, open-label, dose-escalation trial was performed in order to determine the dose-limiting toxicity of cisplatin and doxorubicin. The drug was administered intraperitoneally as pressurized aerosol chemotherapy (PIPAC) in women with recurrent OC with authors reporting that PIPAC with cisplatin/doxorubicin can be safely used at an IP dose of 10.5 mg/m2 and 2.1 mg/m2, respectively, while the systematic toxicity of this therapy was reported to be low. PIPAC maintained quality of life in patients with recurrent cancer and PC was supported to be a safe, evidence-based and effective treatment for women with OC and PC beyond the third line of systemic chemotherapy (17,18).

The angiogenic gene PLXDC1 was deregulated in order to be tested as anti-angiogenic tumor therapy for EOC by Kim et al. PLXDC1 small interfering siRNA (siRNA) - incorporated chitosan nanoparticle (CH-NP/siRNA) coated with hyaluronic acid (HA) was developed to target the CD44 receptor on EOC. The authors reported that HA-CH-NP/siRNA inserted intraperitoneally, is a highly selective delivery platform for siRNA, and has an anti-angiogenetic effect on EOC (19).
In the same year, a biodegradable polymer poly (ethyleneglycol) (PEG)-poly (lactic acid)(PLA)-folate (FA-PEG-PLA) was prepared in order to synthesize an active-targeting, water-soluble and pharmacomodulated photosensitizer nanocarrier, for intraperitoneal targeting of ovarian cancer. Increase levels of the drug in ascitic tumor tissues were observed - 20-fold ($P < .001$) -, which underscored the effect of a regional therapy approach with folate targeting. Moreover, the HB-loaded micelles were mostly distributed in liver and kidney. The results of this study showed that the newly developed PDT photosensitizer HB/FA-PEGPLA micelles have a high drug-loading capacity, a controlled drug release effect, good biocompatibility, and antitumor effect (20).

Becker et al. investigated the safety and tolerability of a regimen consisting IV docetaxel (75 mg/m2) and IP cisplatin - 75 mg/m2 administered in day 1- and paclitaxel - 60 mg/m2 administered in day 8- with granulocyte colony-stimulating factor. The specific docetaxel-based IP chemotherapy regimen, administered in 60 patients, demonstrated an improved safety profile compared to GOG172. Median progression-free survival (PFS) was 25.5 months, OS for all patients was 56.8 months, while, complete response was achieved for 88% with 43% of the patients being currently without evidence of the disease (21).

Westrom et al., studied two tumor models based on the cell lines, ES-2 and SKOV3-luc, with different growth patterns in mice with intraperitoneal OC. Intraperitoneal treatment with 224Ra-microparticles was administered, with the study resulting in increased antitumor effect, a considerably reduced tumor volume and an overall survival benefit. It was observed that only a few kilobecquerels per mouse were enough to yield therapeutic effects. The maximum dosage was up to 1000 kBq/kg and was well tolerated. The authors concluded that intraperitoneal α-therapy with 224Ra-microparticles presented potential effectiveness for the treatment of peritoneal micrometastases in OC (22).

Lee et al., presented a study in Cancer chemotherapy and pharmacology journal, where IP and IV chemotherapy were compared in patients with advanced OC after neoadjuvant chemotherapy (NACT) and interval debulking (IDS) or primary debulking surgery (PDS). Although the authors did not reveal any advantage with IP chemotherapy use after NACT and optimal IDS, they also revealed a survival advantage for IP chemotherapy following PDS (23).

Padmakumar et al. (23) studied the pharmacokinetic advantages offered by IP chemotherapy. Indwelling catheters were used in order to test the ability of retaining high concentrations of the drugs inserted, with high peritoneum/plasma ratios in the area under the drug concentration-time curve (AUC). It was finally observed that the metronomic dosing strategy can increase therapeutic efficacy with a continuous, low dose insertion of chemo-drugs. Based on their results, the authors also suggested that non-catheter based, intraperitoneal therapy retaining the peritoneal-drug levels, offers less systemic levels and therefore less toxicity. This method of administration offers significant survival advantages as a patient-compliant therapeutic strategy. Moreover, suturable-implantable devices based on metronomic dosing, or along an eluting drug offers a sustain release effect at low doses and can be implanted surgically post-debulking for treatment of refractory EOC patients (24).

DISCUSSION

Even though conventional intravenous administration of chemotherapy has proven to be one of the most effective treatment options for different cancer subtypes, the need for improving overall survival encourages the search for newer therapeutic methods. Until now, the most important prognostic factor for OC survival is the ability to achieve optimal cytoreduction with no residual disease. Lymph node involvement has been reported to be common in advanced OC representing an established prognostic factor. Moreover, extensive lymphadenectomy and the number of positive nodes have been observed to be associated with survival of patients with advanced OC while current recommendations regarding extensive lymphadenectomy in advanced OC remains debatable (25).

The use of intraperitoneal chemotherapy seems to play a key role in postoperative progression and OS in patients with OC. It has been reported that increased temperature in HIPEC within an appropriate range could improve even more these outcomes. Even though further trials are required to determine the role of HIPEC with a sustain release effect in primary and recurrent settings, so as to become even more applied for advanced OC, we believe that the combination of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are proving more and more that they should be considered as a therapy of choice for the management advanced OC.

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