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EFFICACY OF HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY IN OVARIAN CANCER IN ADULT WOMEN (RS)

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Abstract
Context: In ovarian cancer, cytoreductive surgery is the treatment of choice, followed by adjuvant chemotherapy; where, hyperthermic intraperitoneal chemotherapy controls residual disease, with the combination of physical (thermal) and chemical (chemotherapeutic) methods prior to the formation of adhesions.
Objective: To determine the efficacy of hyperthermic intraperitoneal chemotherapy in ovarian cancer in adult women.
Procedures: Systematic review of primary studies published in PubMed, Scopus and Web of Science from 2013 to 2023, in Spanish and English.
Results: A total of 133,393 articles were obtained, 108 were selected after the first reading, later considering the inclusion and exclusion criteria, 9 studies were used for the present review. The categories hyperthermic intraperitoneal chemotherapy, Cytoreductive Surgery, Survival, Endothelial Ovarian Cancer are described.
Conclusion: Research results support the efficacy of HIPEC as a promising therapeutic approach for ovarian cancer treatment. , demonstranting an overall survival of 35 months and progression – free survival of 15.6 months.

Keywords: Chemotherapy, Efficacy, Hyperthermic, Intraperitoneal, Ovarian Cancer.

INTRODUCTION

Statistically, ovarian cancer ranks seventh in incidence in women between the ages of 20 and 74 [(1,3)], with an estimated mortality rate of 8.4 [(4)], which is approximately 168,752 women in the world [(5)]. In numerous studies, it is considered "the silent killer" because in the first instance it presents vague and

non-specific symptoms, which leads to confusion with other diseases, thus delaying early diagnosis[3,5].

In Latin America, the incidence of ovarian cancer is 9.2%, with a mortality rate in women of 7.3 per 100,000, compared to the United States, where the incidence of cases and the mortality rate are 12.6% and 8.8%, respectively [1,6,7], all of this depending on a myriad of Factors including infiltration and metastasis of the disease at the time of diagnosis [8].

Damián – Aucancela M, et al., [6] In their study conducted in 2020, they describe how more than 313 cases were diagnosed worldwide thousand Cases More than 207,000 of them died of ovarian cancer, which showed that late diagnosis of this disease unfortunately leads to death. This situation was observed with greater prevalence in elderly women, who avoided follow-up check-ups and resorted to self-medication in the face of mild symptoms. This supports the importance of conducting clinical research on ovarian cancer, which allows the identification of important aspects of this disease, such as new methods of detection, diagnosis, treatment and prevention in different countries and geographical areas of the world [6].

Ovarian cancer currently does not have screening tests that allow an early diagnosis, which is why it is identified late in 68% - 75% of cases, with an average age of diagnosis of 65 years, presenting in 5 years in stage IV a survival of less than 10% while stage IA of 80%. In this context, in 2016, the FederationInternationalofGynecologyThe International Institute of Obstetrics (FIGO) determined that the survival of women with ovarian cancer can be affected by age, the general condition of the patients, the feasibility of surgery with total resection and time of diagnosis. [9].

In recent years, the survival rate in women with ovarian cancer has been the subject of analysis, as less radical treatments have caused a positive change in this parameter, bringing the attention of the medical class to the complications or sequelae that treatments may generate in the female population, a clear example of this. It is the care and preservation of fertility, a situation that is considered during treatment, without this meaning a decrease in cure and survival rates [6].

Chemotherapy, considered one of the treatments to be used in ovarian cancer, uses drugs that contain platinum in their composition, such as cisplatin and carboplatin, which on some occasions may not fulfill their purpose, due to resistance to their main component. There are numerous experimental studies that try to identify new drugs or therapies for cancers with cells resistant to normal chemotherapies, in which the specific cellular mechanisms that generate resistance are analyzed in detail [1,6].

Chemosensitivity and the degree of cytoreduction achieved in surgery are the main influences on the prognosis of advanced ovarian cancer (14,15). In its surgical treatment, there are several important clinical situations to analyze, such as: rescue surgery in women with primary suboptimal surgery, interval surgery or secondary cytoreductive surgery after systemic neoadjuvant chemotherapy, primary cytoreductive surgery without systemic neoadjuvant chemotherapy (2,3,10,13,14).

These studies, in addition to looking for new drugs, investigate the forms or routes of administration that will be used for the treatment of ovarian cancer caused by resistant cells, leaving aside traditional routes such as the intravenous route, giving way to the administration of carboplatin superior to cisplatin. In addition, the administration of chemotherapy during surgery, with the use of drugs at high temperatures, emerges as another alternative in the treatment of ovarian cancer, a therapy called HIPEC, a novel technique, which has generated satisfactory results, with greater advantages, survival rates and fewer complications and sequelae [6].

Sugarbaker is the one who made the proposal for the administration of HIPEC for ovarian cancer, with the purpose of treating residual microscopic disease at the same time of surgery [11]. This researcher showed that hyperthermic intraperitoneal chemotherapy increases the tumor response to cytostatics, enhancing the cytotoxic effect and increasing its action in tissues, due to the direct antitumor effect caused by heat [12].

The benefit of cytoreductive surgery is greatest when combined with HIPEC, ranging from two-year to eight-year survival on combination therapy. In women with recurrent ovarian cancer (ROC) after hyperthermic intraperitoneal chemotherapy, the median overall survival is 34.9 months [13]. For the administration of hyperthermic intraperitoneal chemotherapy there are a wide variety of criteria to be

considered for its use, for example, the definition of optimal surgery, the clinical picture in which it is indicated, the chemotherapy used and its dose, the infusion time and the temperature used (37 °C – 46 °C)[13,14].

Chemosensitivity and the degree of debulking achieved in surgery are the main influences on the prognosis of advanced ovarian cancer [14,15]. In its surgical treatment, there are several important clinical situations to analyze, such as: rescue surgery in women with primary suboptimal surgery, interval surgery or secondary cytoreductive surgery after systemic neoadjuvant chemotherapy, primary cytoreductive surgery without systemic neoadjuvant chemotherapy [2,3,13,14].

The purpose of this review is to describe the efficacy of HIPEC for ovarian cancer in adult women, by determining overall survival and progression-free survival after therapy, with the aim of increasing the quality of life of patients, their families, the community, and the local and national health system.

METHODOLOGY

1) Study Design

A systematic review was carried out, following the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guideline, the data were obtained from the databases mentioned below, to determine the efficacy of HIPEC in ovarian cancer in adult women.

2) Research Question

How effective has HIPEC been as a treatment for ovarian cancer in adult women?

- **Patients**: Adult women with ovarian cancer.
- **Intervention:** HIPEC.
- **Comparison: Between** PFS and OS in patients with ovarian cancer treated with hyperthermic intraperitoneal chemotherapy.
- **Results:** Progression-free survival and overall survival.

3) Inclusion Criteria

- Studies in English and Spanish.
- Studies containing a population: adult women.
- Original articles, randomized clinical trials, and pilot studies.
- Articles with studies in humans.
- Articles related to hyperthermic intraperitoneal chemotherapy.
- Articles with studies of progression-free survival (PFS) or overall survival (OS) of hyperthermic chemotherapy in ovarian cancer.

4) Exclusion Criteria

- Articles containing narrative reviews, systematic reviews, individual study, letters to the editor, meta-analysis.
- Articles in patients with colorectal cancer.
- Articles in other languages.
- Items that do not meet the established variables.

5) Databases

A compilation of scientific studies was carried out in the databases Scopus (https://www.scopus.com/), Web Of Science (https://www.webofscience.com/) and PubMed (https://pubmed.ncbi.nlm.nih.gov/).

6) Search Terms or Keywords

The search terms used were obtained from the MeSH (Medical Subject Headings) and are: Chemotherapy, Efficacy, Hyperthermic, Intraperitoneal, Ovarian Neoplasms, Progression-free, overall survival.

7) Search Sentence

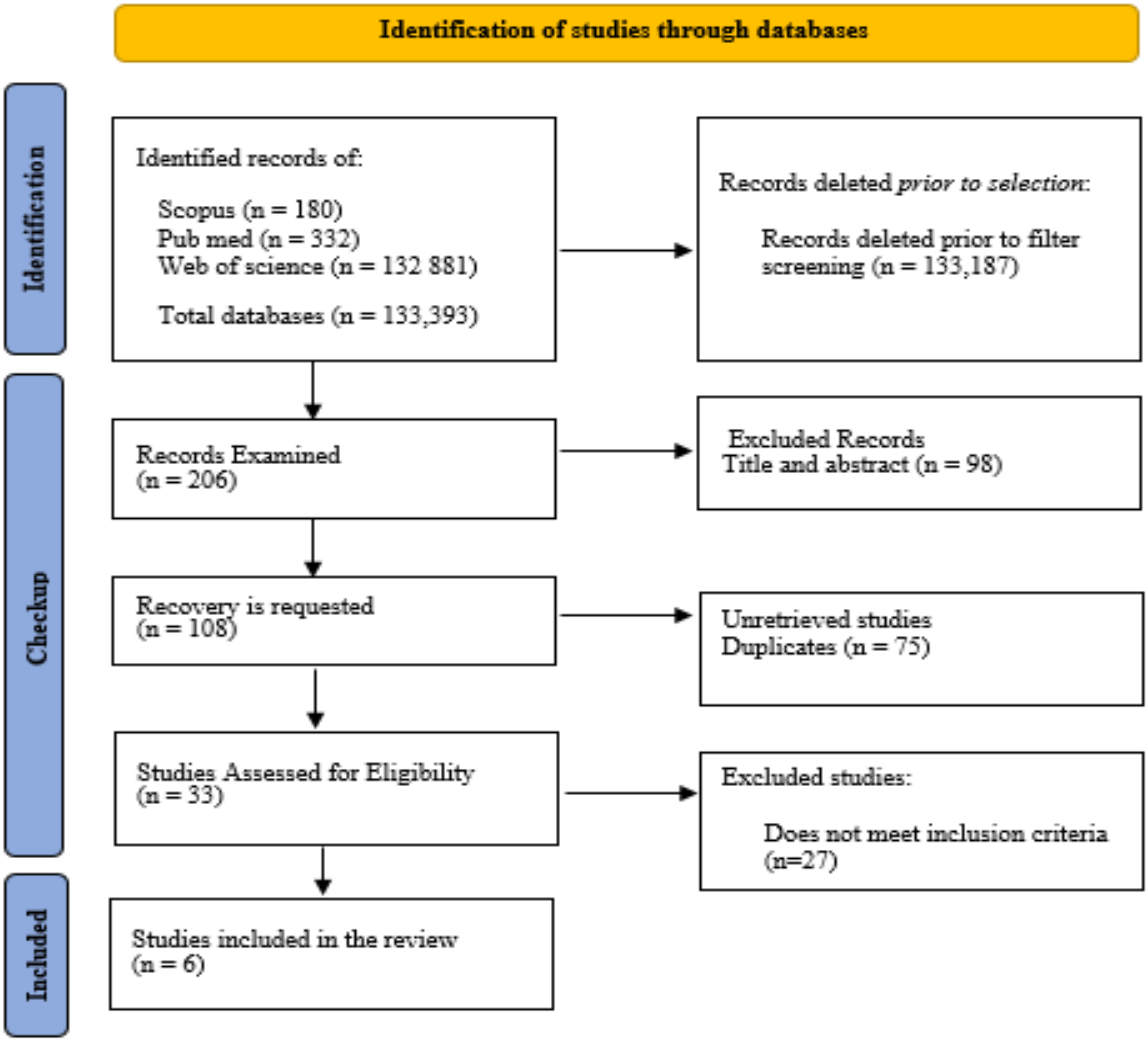
For the elaboration of this systematic review, the PRISMA method was used, by means of a critical analysis. Obtaining from MeSH the keywords that were linked for the search, specific terms were applied in English Progression-free OR overall survival OR efficacy (Hyperthermic Intraperitoneal Chemotherapy OR HIPEC) AND Ovarian Neoplasms NOT Colorectal Neoplasms in the PubMed, Web Of Science and Scopus databases from January 1, 2013 to January 2023 in English and Spanish. The inclusion criterion was the relationship of the search terms in the studies carried out with survival, excluding duplicate and irrelevant studies, **Figure 1**, where articles from indexed journals Scientific Journal Rankings – Scimago (SJR) were taken into consideration; a contingency table was used for the collection of information.

8) Bias Assessment

Bias was assessed using the Risk Of Bias In Non - randomised Studies – of Interventions (ROBINS-1) tool, which allowed us to classify and analyse the risk of bias of each of the studies used in the research. This tool determines whether studies have serious, moderate, or low judgment using 7 domains (first confounding domain, second participant selection domain, third intervention classification domain, fourth planned intervention deviation domain, fifth data loss domain, sixth outcome measurement domain, and seventh reported outcome selection domain) **Figure 2-3**.

RESULTS

Figure 1 *PRISMA Flow Algorithm from the Systematic Review*



Source: Review Sheets

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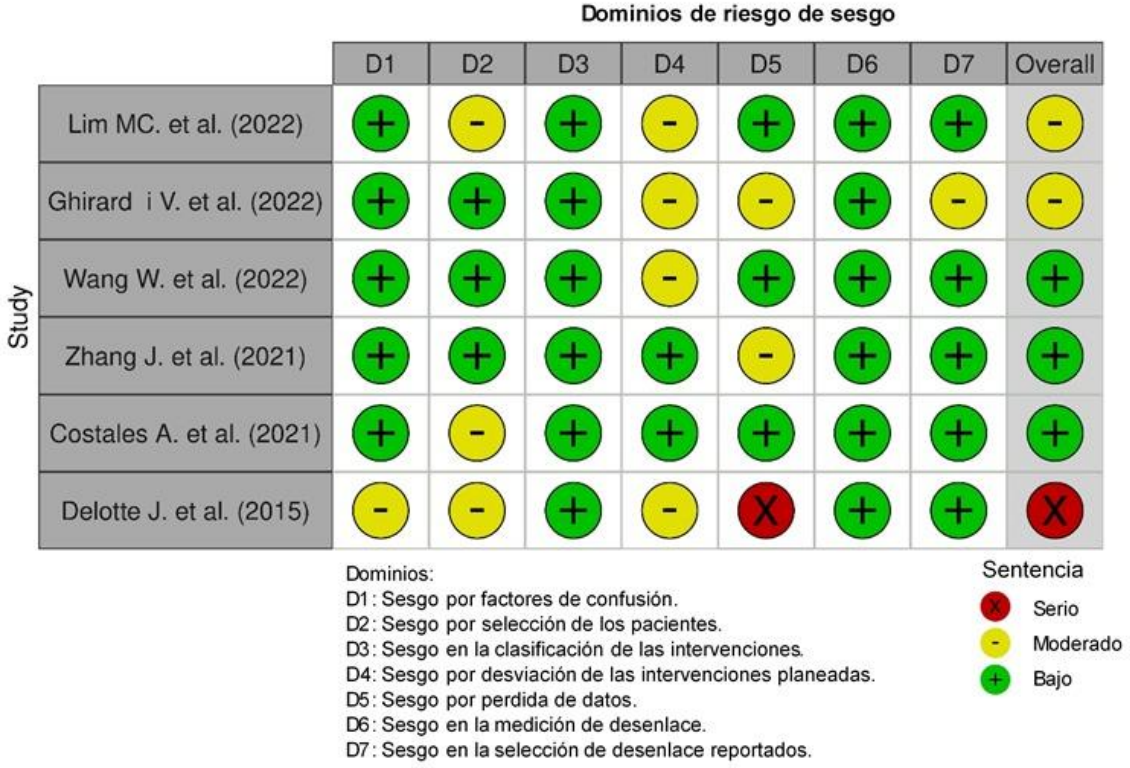
After the search process in the databases, a total of 133 393 articles were obtained, of which 180 belonged to Scopus, 332 to Pubmed and 132881 to Web of Science, consequently filters were placed, leaving a total of 206 studies for analysis. Next, titles and abstracts were read, excluding 98 studies that did not comply with the established variables. After this step, 108 articles were recovered, however, 75 were eliminated because they were duplicates, and at that time there were 33 relevant to the present review. As a next step, the full text was read, discarding 27 papers because they did not meet the inclusion criteria, leaving 6 articles in English that included a total population of 1605 women treated with intraperitoneal chemotherapy in ovarian cancer, in addition, they met the objectives of describing the efficacy of HIPEC in ovarian cancer. **Table 1** shows the bibliographic records used for data analysis.

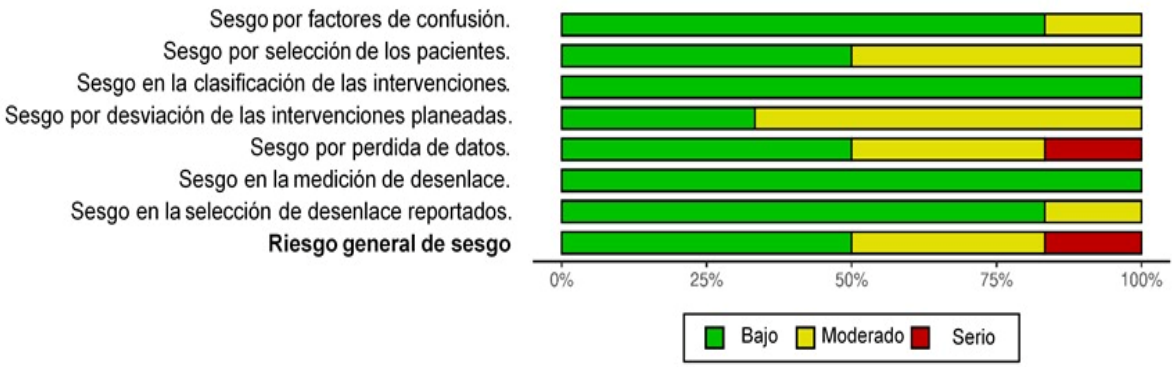
Quality Assessment

Figure 2 *Graphical Summary of Bias Risk Using the ROBINS-1 Tool*



Source: Graficar ROBINS-1
Authors: Vanessa Isabel Abad Barahona, Flor Dalila Minchala Sucuzhañay

Figure 3 *Graphical overview of bias risk using the ROBINS-1 tool*



Source: Graficar ROBINS-1
Authors: Vanessa Isabel Abad Barahona, Flor Dalila Minchala Sucuzhañay

Assessment of bias in articles

In the present research, the risk of bias and its eligibility criteria were evaluated with the ROBINS-I tool, which evaluates 7 domains. Regarding the first domain of confounding factors, 5 studies have low risk and 1 article has moderate risk. In the second participant selection domain, 3 were at moderate risk and the other 3 studies were at low risk. The third domain evaluates the intervention, with 6 studies achieving a low risk. In relation to the fourth domain of deviation from planned interventions, 4 articles were at moderate risk and 2 were at low risk. In the fifth domain of data loss bias, 1 was obtained as a serious risk, 2 as a moderate risk, and 3 as a low risk. In the sixth domain of outcome measurement, 6 studies were at low risk. Finally, in the seventh domain of selection of reported outcomes, 1 moderate and 5 with low risk were obtained. In general, it is evident that 3 articles give a low risk, 2 articles are moderate and 1 article presents a serious risk, thus presenting the articles a low risk of bias. **Figure 2 -3**.

Table 1Characteristics of the selected studies

Authors	Theme	Objective	Type of study	Sample	SLP & SG	RESULTS
Lim MC. et al. (2022) South Korea [17].	Survival After Hyperthermic Intraperitoneal Chemotherapy and Primary or Interval Cytoreductive Surgery in Ovarian Cancer	To assess the clinical benefit of HIPEC following primary maximum CRS in women with stage III or IV primary advanced ovarian cancer.	Randomized Clinical Trial	184 patients with stage III or IV ovarian cancer with residual size	HIPEC Progression-free survival Overall Survival	In 184 women, they had a PFS of 18.8 months. (IQR, 13.0/-/43.2 months) in the control group and 019.8 months /(IQR, .52). In the post-interval neoadjuvant chemotherapy CRS subgroup, the median PFS was 15.49 months (IQR, 10.6-21.1 months) in the control group and 17.4 months (IQR, 13.8/ /31.5 months) in the HIPEC group (HR for disease progression death, 0.60; 95% CI, 0.37-0.99; P = 0.04), and OS was 48.2 months (IQR, 33.8-61.3 months) in the control group and 61.8 months (IQR, 46.7 months to unreported) in the HIPEC group (HR 0.53; 95% CI, 0.29-0.96; p=.04).
Ghirardi V. et al. (2022) Italy [18].	Hyperthermic Intraperitoneal Chemotherapy (HIPEC) After Primary Cytoreductive Surgery in Advanced Epithelial Ovarian Cancer: Is BRCA Mutational Status Making a Difference?	To assess the effect of HIPEC after CRS on COCs based on the patient's breast cancer gene (BRCA) mutational status.	Retrospective case-control study	70 patients aged 18 to 70 years with stage IIIB or greater ovarian cancer with BRCA mutations	HIPEC Progression-free survival Overall Survival	In their study, they indicate that PFS (p = 0.968) and overall survival (OS) (p = 0.789) Survival analysis based on HIPEC administration and BRCA mutational status showed improved PFS (p/= 0.011) and OS (p/=/0.003) in patients with BRCA mutation No disparity in intraoperative analysis (p/= 1.0) or early postoperative complications (p = 0.920).
Wang W. et al. (2022) [19].	Effect of neoadjuvant chemotherapy combined with intraperitoneal chemotherapy after tumor cell reduction at intervals on the prognosis of advanced epithelial ovarian cancer.	To investigate the effect of neoadjuvant chemotherapy combined with intraperitoneal chemotherapy after tumour cell reduction in advanced epithelial ovarian cancer	Retrospective study	210 patients with advanced ovarian cancer treated with neoadjuvant chemotherapy treated with HIPEC	HIPEC Progression-free survival Overall Survival	HIPEC and absence of gross residuals were independent factors of survival, with HRs of 0.560 (95% CI 0.342-0.918; p=0.022) and 0.578 (95% CI 0.377-0.887; p=0.012). There were no independent factors associated with OS. Significant differences in PFS were detected between the R0 + IP group, the R0 + IV group, the non-R0 + PI group, and the non-R0 + IV group. In patients with R0 tumor reduction, PI patients showed significantly better PFS. Cycles of neoadjuvant chemotherapy (≤3 and >3) were not the factors influencing PFS or OS and did not affect platinum-sensitive relapse or platinum-resistant relapse. The decrease in postoperative CA125 was not associated with platinum-sensitive recurrence or platinum-resistant recurrence.
Zhang J. et al. (2021) China [21].	Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival with acceptable	To assess the safety and efficacy of CRS plus HIPEC as first-line treatment in patients with advanced	Prospective study	In 100 women with stage III-IV COA	HIPEC Overall survival.	The complete debulking score (WC) had a median of 1(0-3). Median OS was 87.6 (95% CI 72.1-103.0) months, and 1- to 5-year survival was 94.1%, 77.2%, 68.2%, 64.2%, and 64.2%, respectively.

	safety for advanced ovarian cancer: a clinical study of 100 patients.	ovarian cancer (AOC).				
Costales A. et al. (2021) [22].	Effect of Platinum Sensitivity on the Efficacy of Hyperthermic Intraperitoneal Chemotherapy in Recurrent Ovarian Cancer	To examine whether survival was similar regardless of platinum sensitivity.	Retrospective Study	48 patients with platinum-sensitive or recurrent OCD	HIPEC Recurrence-free survival Overall Survival	The median PFS in thepatientswith R0 was 22.3 months in patients with PS and 11.1 months in patients with RP (p = 0.017), respectively. PR patients had an overall survival of 26.9 months, whereas it had not been achieved in PS patients.
Delotte J. et al. (2015) France [27].	Hyperthermic intraperitoneal chemotherapy for the treatment of recurrent ovarian cancer in older women	To assess the morbidity and survival associated with combined cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of recurrent ovarian cancer in women aged 70 years and over.	Retrospective single-center study	15 women over 70 years of age with recurrent ovarian cancer treated with CRS and HIPEC.	HIPEC SLP	Overall survival of 35 months, with PFS of 15.6 months. Subgroup analysis of the peritoneal cancer index showed a statistically significant difference in disease-free survival for a peritoneal cancer index ≤13 (p = 0.036). A trend towards improvement in the disease ( )

Source: *Review Sheets*

Authors: Vanessa Isabel Abad Barahona, Flor Dalila Minchala Sucuzhañay Results

DISCUSSION

The systematic review on the Efficacy of HIPEC for ovarian cancer during the period between 2013 and 2023, shows how this health problem constitutes a challenge for all levels of care, both public and private; each study describes the relationship of HIPEC in the treatment of EOC and survival, in some the existence of complications and their interference in the survival of the population studied [1,3,7,9,11].

The success of the treatment of ovarian cancer with the administration of HIPEC results from the local contact that the drug has with the tumor tissue, and it is necessary to consider some contributing factors such as the time of contact with the tissues, the ability to penetrate them, the permeability of the drug, the size of the tumor and the potentialization given by hyperthermia [20,23,24].

As has been mentioned repeatedly, the determination of the drugs to be used in intraperitoneal chemotherapy depends on the location of the primary tumor, and especially on whether it is delimited or whether there are already infiltrations or metastases. Several lines of HIPEC have been used in the aforementioned studies according to the primary origin of ovarian cancer, thus we have, in peritoneal pseudomyxoma the use of cisplatin + mitocin at 42ºC and in ovarian cancer doxorubicin + cisplatin at a temperature of 42ºC [16,22,25].

In the research carried out, intra-abdominal chemotherapy evidences its effectiveness as a therapy for tumors at the cavity level, reaching high concentrations of tumor cytotoxic agent at the regional level, thus reducing side effects and thus in most cases complications and disorders in the quality of life of women who received the treatment [22,24]. With HIPEC, tissue concentrations of 20 to 400 degrees higher than those administered by traditional intravenous route have been achieved; [22,25] This is achieved by immediately using post-surgery therapy, prior to tumor cell entrapment with fibrins and the creation of intra-abdominal compartments by surgical adhesions [27].

Despite the significant advantages of HIPEC, different studies report complications such as post-surgical bleeding, respiratory failure, bone marrow suppression, perforations, dehiscence of digestive sutures, intestinal fistulas, intra-abdominal abscesses, methicillin-resistant Staphylococcus aureus (MRSA) infections, and pulmonary embolism caused by up to 10% of surgical reinterventions [18-23].

Survival has been reported in women with EOC overall of 81%, 74% and 53% at 12, 24 and 60 months. Survival rates for each diagnosis for the same periods were 87%, 82%, and 47% in patients with pseudomyxoma, and 77%, 72%, and 57% in patients with CRC (log-rank 0.371, p=0.543) [16].
In another study, PFS was 18,8 months in the control group and 19.8 months in the HIPEC group (p = 0.43), and overall survival of 61.3 months (IQR, 34.3 months to unreported) in the control group and 69.5 months (IQR, 45.6 months to unreported) in the HIPEC group (p=.52) [17].
In relation to the SLP (*p=0,*968) and SG (*p=0.789)* There is no divergence.Survival analysis based on HIPEC administration and BRCA mutational status showed PFS (*p=0.011) and OS (p=.003) improved in BRCA-mutant patients when compared to wild-type patients when HIPEC was not administered. There is no disparity in the* Intraoperative analysis (*p=1.0) or early postoperative complications (p=0.920)* [18].
Intraperitoneal chemotherapy and absence of gross residuals were independent factors of survival, with HRs of 0.560 (95% CI: 0.342-0.918; p=0.022) and 0.578 (95% CI: 0.377-0.887; p=0.012) [19].
Whereas participants in one study were divided into 2 groups based on HRR mutation status and randomized to receive CRS + HIPEC. The patients then received regular chemotherapy and follow-up. In this study, HIPEC and CRS only report the presumption that HIPEC and CRS improve PFS in women with platinum-sensitive recurrent EOC with HRR mutation compared to patients without HRR mutation [20].
However, in a study of 152 patients with EOC underwent HIPEC in 39 hospitals, and 20,014 patients underwent surgery without HIPEC in 256 hospitals. During index admission, patients undergoing HIPEC had a longer mean length of stay (8.4 vs. 5.7 days, p < 0.001) and a higher percentage of ICU admissions (63.1% vs. 11.0%, p<0.001) and complication rates (RR=1.87, p=0.002). Direct costs of admission (21,825 vs. 12,038, p<0.001) and direct cost index (observed/expected costs) (1.87 vs. 1.11, p<0.001) were higher in the HIPEC-exposed population. No hospitalization deaths or readmissions were identified at 30 days after HIPEC [23].
Overall survival is 35 months, while PFS is 15,67 months . When the peritoneal cancer index was analyzed in the subgroups, a statistically significant difference was observed in disease-free survival for a peritoneal cancer index ≤13 (p=0.036). In addition, a tendency to improve PFS was observed when the Cytoreduction Completeness Score was equal to 0 (p=0.0915) [27].

CONCLUSION

The results obtained in the research support the efficacy of HIPEC as a promising therapeutic approach as a treatment in ovarian cancer. In the different studies reviewed and the data collected, they consciously demonstrate that hyperthermic intraperitoneal chemotherapy offers significant advantages related to PFS and OS of the disease and significantly improves women's quality of life. More research is needed in the area because much of the literature comes from countries in Asia and Europe, and there is not much literature on the subject in the Americas.

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