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Cytoreductive Surgery (CRS) Combined With Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Platinum-Sensitive Recurrence Epithelial Ovarian Cancer With HRR Mutation: A Phase III Randomized Clinical Trial

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Abstract

Background: Epithelial ovarian cancer (EOC) remains the leading cause of gynecologic cancer death worldwide due to the high recurrence rate. Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is an alternative modality for platinum-sensitive recurrent EOC. The latest studies demonstrate homologous recombination-related (HRR) mutation status increases the sensitivity to platinum-based chemotherapy drugs in EOC. However, the molecular analysis of recurrent EOC patient benefits from HIPEC is unknown. Thus, we aimed to evaluate the efficacy and safety of CRS combined with HIPEC for platinum-sensitive in recurrent EOC with HRR mutation. **Methods:** This is a phase III randomized controlled clinical trial in patients with platinum-sensitive recurrent EOC. Participants were divided into 2 groups based on the HRR mutation status and randomized to receive CRS + HIPEC. The patients then received periodic chemotherapy and follow-up. **Results:** The primary objective of this study was to evaluate the effect of CRS + HIPEC compared to CRS alone in patients with a platinum-sensitive recurrent EOC stratified for HRD status. We hypothesize that the addition of HIPEC to CRS improves the progression-free survival (PFS) of platinum-sensitive recurrent EOC patients with HRR mutation compared with patients without HRR mutation. **Conclusion:** Recurrent EOC has a poor prognosis due to implantation and metastasis in the abdominal cavity. Intraperitoneal chemotherapy reduced seeding by removing free tumor cells. HIPEC utilizes physical and biological properties to significantly increase the clearance rate of tumors. Van Driel WJ et al proposed that HIPEC using platinum-based chemotherapy improves the survival of patients with ovarian cancer. HRR mutation, as a common pathogenic mutation in ovarian cancer, has a predictive effect on the platinum sensitivity of ovarian cancer patients. Whether lobaplatin-based HIPEC will play a greater role in ovarian cancer patients with HRR mutations is currently unknown.

Keywords

HIPEC, HRR, HRD, EOC, recurrent ovarian cancer

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Abbreviations

CRS, cytoreductive surgery; CTCAE 6.0, Common Terminology Criteria for Adverse Events version 6.0; DP9, 9-month progression-free survival rate; DP12, 12-month progression-free survival rate; EOC, epithelial ovarian cancer; HRD, homologous recombination deficiency; HRR, homologous recombination-related; HIPEC, hyperthermic intraperitoneal chemotherapy; KPS, Karnofsky performance status; NHEJ, non-homologous end joining; OS, overall survival; PFS, progression-free survival; SAEs, serious adverse events

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Introduction

Ovarian cancer is the leading cause of gynecologic deaths worldwide.[1] In 2020, it was estimated that 21,750 new cases and 13,940 deaths would occur in the United States and 29,000 deaths in Europe.[2,3] Although there have been advances in treating epithelial ovarian cancer (EOC), reoccurrence remains largely fatal.[4] Of those newly diagnosed advanced ovarian cancer patients, more than 70% will have a recurrence within the first 5 years.[5,6] Since the clinical need is greatest for these patients, new treatments for ovarian cancer are needed.

For recurrent ovarian cancer patients, the most effective treatments include surgery to minimize tumors and the use of platinum-based chemotherapy agents.[7] Intra-abdominal chemotherapy provides a more intuitive distribution of the drug over the surface of the peritoneum than intravenous chemotherapy, resulting in a higher survival rate.[8] Intra-abdominal chemotherapy, delivered after warming during surgery, is called hyperthermic intraperitoneal chemotherapy (HIPEC). Warming increases the penetration of chemotherapy drugs and their sensitivity.[9] Platinum chemotherapy drugs are primarily used in HIPEC.

The homologous recombination-related (HRR) gene is a double-stranded DNA injury repair pathway with high fidelity that, when damaged, results in homologous recombination deficiency (HRD).[10] HRR mutations significantly prolong progression-free survival (PFS) and overall survival (OS) time in ovarian carcinoma.[11] Drugs targeting HRD are used clinically.[12] HRD is a predictive factor for PFS and OS after platinum therapy and indicates platinum sensitivity.[13] However, for recurrent ovarian cancer patients with HRR mutations, it is not clear whether platinum-based HIPEC is beneficial.

Here we present a randomized controlled open-label prospective trial of patients diagnosed with recurrent ovarian cancer and treated with the application of HIPEC. The study analyzed the relationship between HRR gene status and HIPEC efficacy. We expect HIPEC to significantly extend PFS in patients with recurrent ovarian cancer with HRR mutations.

Materials and Methods

Study Design

A prospective randomized phase III clinical study was performed. The patients were divided into 2 groups according to the HRR gene mutation status. This study was conducted by the Zhongnan Hospital of Wuhan University, China.

Primary Objectives

The primary objective of this study was to evaluate the effect of cytoreductive surgery (CRS) + HIPEC compared to CRS alone for patients with a platinum-sensitive recurrent EOC stratified by HRD status.

Secondary Objectives

1. To assess the 1-, 3-, and 5-year survival rates of patients.
2. To assess the quality of life and pain in study patients.
3. To assess the toxicity of treatment, including nephrotoxicity.
4. To assess the incidence of postoperative complications in study patients.

Inclusion Criteria

Eligible patients must meet all of the following criteria to be included in the trial:

1. Age: 18–75 years old.
2. The initial disease was EOC, fallopian tube cancer, or primary peritoneal cancer; more than 6 months have passed since the end of the initial treatment, and there was a recurrence in the abdominal cavity that can be resected without distant metastasis. However,2 exceptions were allowed: (1) independent pleural metastasis, which was sensitive to platinum-based class of second-line chemotherapy drugs or (2) retroperitoneal lymph nodes or inguinal lymph nodes that were individually involved and could be surgically removed.
3. Karnofsky performance status (KPS) > 50 or World Health Organization performance status scores <2.
4. Surgery could completely remove the lesion, or the maximum diameter of the residual lesion after surgery did not exceed 0.5 cm.
5. Peripheral blood white cell counts were $\geq 3.5 \times 10^9$/L, platelet counts were $\geq 80 \times 10^9$/L, and hemoglobin was $\geq 90 \times 10^{12}$/L.
6. There was a normal heart and lung function, with no general anesthesia contraindications for major surgery.
7. Life expectancy $\geq$ 3 months.
8. Participants had to be informed and consent signed before entry into the study. Women of childbearing age were on appropriate contraceptive during the trial

period and until 6 months after the treatment was finished.

Exclusion Criteria

1. History of other cancers (except skin basal cell carcinoma and cervical carcinoma in situ) with recurrence within the past 5 years.
2. Disease progression during chemotherapy treatment.
3. Distant metastasis of tumors.
4. It was expected that 2 or more digestive tract resections would be required at the same time.
5. Cellular components of non-epithelial origin in the histology of ovarian tumors.
6. Allergic to platinum drugs.
7. Liver damage (bilirubin > 1.5 times the normal value, AST or ALT > 3 times the maximum value within the normal range).
8. Renal insufficiency (creatinine >1.5 times the normal value, creatinine clearance rate < 60 mL/min) (measured according to the MDRD method).
9. Application of anti-angiogenic drugs (within 8 weeks before surgery).
10. The existence of cardiovascular or respiratory diseases making the high-volume hydration a contraindication.
11. Patients who could not follow up geographically or psychologically.
12. Incapacitated adults.
13. Women who were pregnant or likely to become pregnant or breastfeeding.
14. Patients who participated in the follow-up of other therapeutic trials.

Withdrawal Criteria

1. Subjects who were required to withdraw from clinical trials.
2. Due to safety reasons, the researcher believed that participation should be suspended.
3. Subjects selected incorrectly.
4. The subject‘s compliance was not within the range of 80% to 120%, and the test protocol was violated.
5. Those with severe or persistent allergic reactions.
6. Those lost to follow-up.

Subjects could freely withdraw from the study at any time without affecting subsequent treatment or follow-up. The investigators recorded the reason for withdrawal and adverse events.

Endpoints

Primary endpoint. The primary endpoint of this study was PFS, which was defined as the time from randomization to the first occurrence of disease progression or death from any cause (Table 1).

Secondary endpoint. Overall survival (OS), 9-month progression-free survival rate (DP9), 12-month progression-free survival rate (DP12), incidence of adverse events, quality of life assessment, and safety are shown in Table 1.

AE Reporting

Serious adverse events (SAEs) during surgery were evaluated according to NCI Common Terminology Criteria for Adverse Events version 6.0 (CTCAE 6.0). All adverse events were reported.

Trial Design

The trial is a prospective, open-label, randomized phase III clinical trial. The trial recruited 280 patients with relapsed EOC. After CRS, test results for HHR mutations were used to place normal and mutated patients randomly into groups (1:1) by computer-generated random numbers for treatment with or without HIPEC. Patients received routine chemotherapy for platinum plus paclitaxel or liposome doxorubicin for 7 to 10 days and were continued to be treated for 8 weeks (Figure 1).

The trial was conducted by the Gynecological Oncology team at Zhongnan Hospital of Wuhan University, Wuhan, China. Our study was approved by The Ethics Committee of the Zhongnan Hospital of Wuhan University (Approval No. 2020107, ethical approval date: May 18, 2020). All patients provided written informed consent prior to enrollment in the study. A patient's motivation was to expect the best treatment outcome.

Table 1. Outcome variables for patients received who CRS combined with HIPEC.

Outcome variables	Evaluation period			Measuring instrument
	Baseline	Posttreatment	Follow-up	
Progression-free survival (PFS) (main outcome)	X	X	X	Days
Quality of life	X	X	X	QLQ C30 and FACTO
Pain	X	X	X	EVA
Toxicity of treatment	X	X	X	CTC-AE
Postoperative complications		X	X	Symptom

Abbreviations: CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

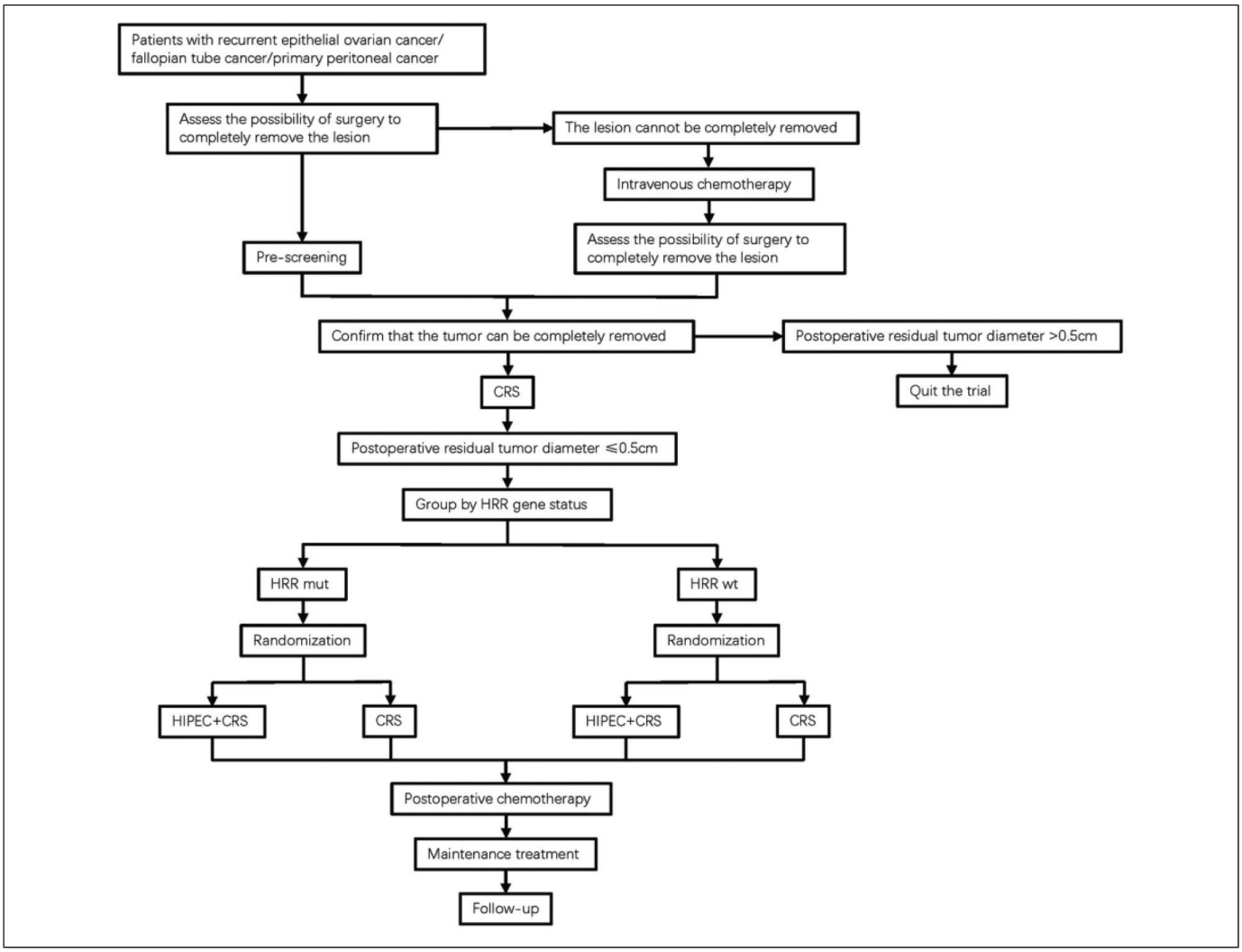

Figure 1. The study flowchart.

Table 2. Clinical and pathological characteristics of recurrence EOC patients.

Variable	Values
Age	Years
Sex	Man/Woman
Duration of symptoms	Months
Work	Employed/Unemployed
Education	No/Elementary school/ Lower secondary school/ Higher secondary school/university
Marital status	Married/Unmarried
Visual problems	Yes/No
FIGO stage	Ia /Ib /Ic/IIa/IIb /IIc /IIIa /IIIb /IIIc/IV
Type	Serous Carcinoma/Clear Cell Carcinoma (CCC)/ Endometrioid/Mucinous
CA125	>35/≤35
Smoking	Yes/No
Medication	Yes/No

Abbreviation: EPC, epithelial ovarian cancer.

Statistical Analysis

Statistical analyses were performed using SPSS version 23.0 (SPSS Inc.). A two-sided $P < .05$ was considered significant.

Results

Participant

All participants had EOC, fallopian tube cancer, or primary peritoneal cancer and relapsed more than 6 months after platinum treatment. Participants were rigorously evaluated prior to surgery. Patients who could not have the tumor completely removed by surgery were assessed again after receiving standard chemotherapy for recurrent ovarian cancer. Patient characteristics were recorded prior to treatment to reduce deviation.[14] These characteristics are shown in Table 2.

If recurrence occurred within 6 months of receiving platinum treatment, the patient was excluded. Patients with tumors after

undergoing preoperative chemotherapy or had remaining tumors larger than 0.5 cm in diameter after surgery were excluded.

Interventions

Patients with recurrent ovarian and peritoneal cancer who were evaluated and determined to be suitable for CRS + HIPEC treatment prior to surgery were kept. Peritoneal cancer index scores were performed prior to surgery and based on a patient's imaging data (Figure 2). Patients who were unlikely to have tumors completely removed by surgery were given preoperative complementary chemotherapy to shrink them. Only patients with residual tumors with diameters less than 0.5 cm were kept in the trial after surgery. Fresh tumor tissues were taken during the operation and frozen for HRR detection. One-hundred seventy-one HRDs were detected by the combined probe-anchored polymerization sequencing method. A patient's blood was used as the control. After satisfactory tumor CRS was completed, intraperitoneal hyperthermic perfusion chemotherapy was started. Perfusion was done by placing the 2 inlet pipes under the diaphragm on both sides and placing the 2 outlet pipes on the left and right iliac fossa. A total of 3000 mL of normal saline was injected into a sterile chemotherapy bag, heated on a chemotherapy instrument, and injected it into the abdominal cavity through an output pump after reaching 43 °C ± 0.5 to achieve hyperthermic perfusion chemotherapy.

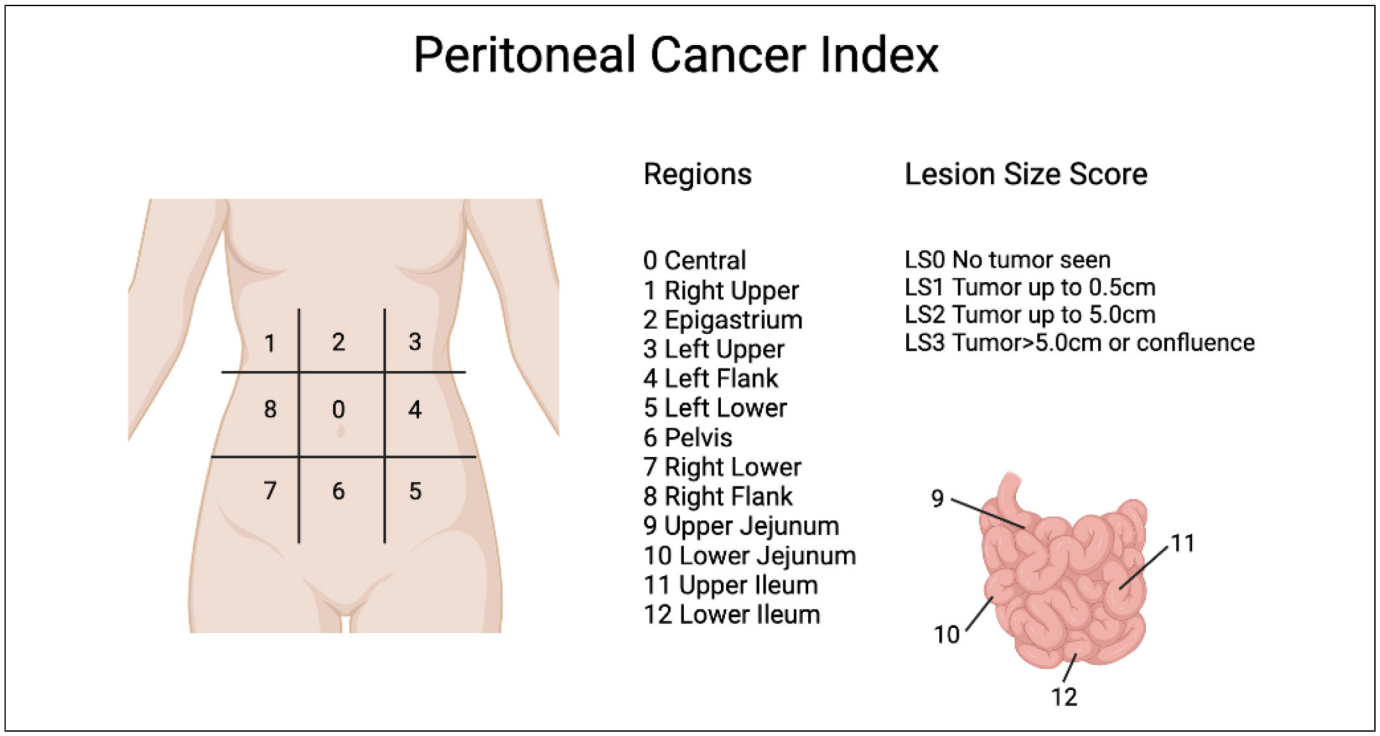

Figure 2. Peritoneal cancer index score.

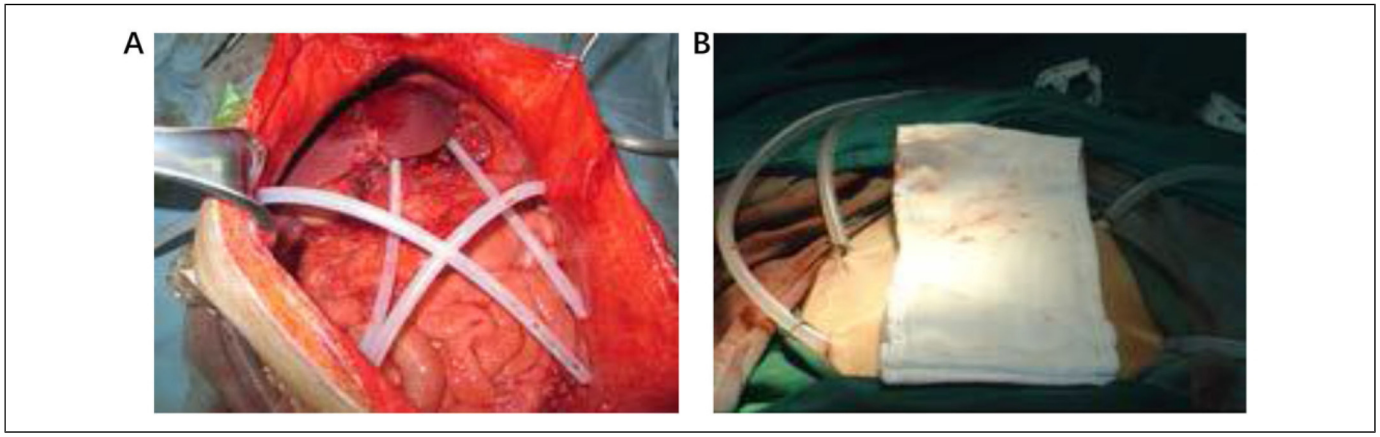

Figure 3. The procedure of hyperthermic intraperitoneal chemotherapy (HIPEC).

Table 3. Study schedule.

	Screening period	Visiting period				Follow-up period		
Visiting time (days)	−28~1	0	3	5	7 to 10	30	60	90	Every 3 months for 3 years
Diagnosis and treatment									
Sign informed consent	X								
HRR detection	X								
Confirm inclusion and exclusion criteria	X								
PCI score	X	X							
Randomization	X								
CRS		X							
HIPEC		X	X	X					
Intravenous chemotherapy					X				
Effective observation									
Survival						X	X	X	X
Tumor markers	X				X	X	X	X	X
Quality of life	X				X	X	X	X	X
Pain	X				X	X	X	X	X
CT	X					Every 9 weeks after CRS			
Safety evaluation									
Blood routine	X				X	X	X	X	X
Liver function	X				X	X	X	X	X
Renal function	X				X	X	X	X	X

Abbreviations: CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; HRR, homologous recombination-related; PCI, peritoneal cancer index.

Lobaplatin 30 mg/m^2 was chosen for HIPEC, and the total chemotherapy time was 60 min (Figure 3). In addition, participants underwent chemotherapy and maintenance therapy, according to current guidelines. Follow-up was every 3 months and lasted for 3 years (Table 3).

Sample Size

The ICON4 study proved the advantages of platinum and paclitaxel in combination with platinum alone in patients who relapsed for the first time after more than 6 months ending initial ovarian cancer treatment.[15] The median survival rate for this trial was 29 months. It assumed that cisplatin-based HIPEC for patients with recurrent ovarian cancer mutations in the HRR gene had increased median OS time at 12 months compared to controls. In this hypothesis, $\alpha = 0$, 05, $\beta = 0.2\%$, 280 cases were included, 204 cases were in the HRR mutation group, and 76 cases were in the HRR non-mutation group, which achieved 80% test power.

Discussion

Ovarian cancer has the highest mortality rate of any gynecological tumor. Over 75% of patients diagnosed with ovarian cancer are at an advanced stage.[16] In addition, after initial treatment, nearly 75% of patients will experience recurrence.[17] The poor prognosis of ovarian cancer is related to implantation and metastasis in the abdominal cavity. Free cancer cells in the abdominal cavity implant into the peritoneum to form small cancer foci, cancer nodules, and extensive implantation and metastasis. As a first-line chemotherapy regimen for EOC, intraperitoneal infusion of chemotherapy drugs significantly improves the prognosis of patients compared with intravenous administration.[8,18,19]

HIPEC has been implemented at several time points in the course of the disease, making its timing an important issue.[20–22] HIPEC takes advantage of the difference in temperature tolerance between cancer cells and normal tissues. Normal tissues can continuously tolerate 47 °C for 1 h, while malignant tumor cells only tolerate 43 °C for 1 h. The perfusion of heated chemotherapeutic drugs at higher temperatures using an abdominal hyperthermia treatment system and its continuous circulation and infusion into the patient's abdominal cavity under these conditions mechanically washes out free cancer cells and peritoneal micrometastasis in the abdominal cavity.[23] Also, HIPEC is believed to act by activating dendritic, cytotoxic T, and natural killer cells to cause immunogenic cell death that increases cell uptake and alters DNA cross-linking.

Several recent studies have attempted to identify the role of HIPEC in recurrent EOC. A phase III clinical trial indicated that among patients with stage III EOC, the addition of HIPEC to interval CRS resulted in longer recurrence-free survival and OS than surgery alone and had similar rates of side effects.[24] There is also a clinical trial that shows that HIPEC improves

the mean survival time and 5-year survival rate of patients with recurrent ovarian cancer.[21] An Italian clinical trial confirmed that the addition of HIPEC may improve survival in patients with platinum-sensitive recurrent EOC.[25]

The choice of the intraperitoneal chemotherapy drug used in recurrent ovarian cancer does not have a consensus.[26,27] We used lobaplatin in HIPEC for recurrent EOC. Lobaplatin has good water solubility and no cross-resistance to cisplatin, making it an ideal drug for HIPEC.[28] It also has strong antitumor activity and less nephrotoxicity.[29]

Changes in the HRR pathway lead to HRD as a result of mutations in genes such as BRCA1/2, RAD51, ATM, MRE11, RPA, and NBS1. The mutation and inactivation of these genes lead to defects in DNA double-strand damage repair. The double-strand damage in these cells subsequently uses error-prone alternative DNA repair pathways, such as non-homologous end joining (NHEJ).[30] Platinum-based drugs work by causing DNA breaks and miscoding. HRD is a predictor of PFS and OS after platinum treatment, and it is also the main indicator of platinum sensitivity.[31] Thermal therapy degrades BRCA2, and platinum causes DNA to break double bonds, potentially benefiting HRR mutation patients with HIPEC.[32] The benefits of HIPEC on PFS in patients with recurrent ovarian cancer HHR mutations need further study.

The need for randomized studies on the use of HIPEC has been reported. This is the first randomized study to identify a relationship between HRR gene status and HIPEC efficacy in recurrent EOC. Our study was open-label, which may have introduced potential deviations. To minimize follow-up bias, we strictly performed regular follow-up and recorded CA125 in detail to measure PFS. The trial was performed at a single center, which may limit the strength of the results. However, surgery is the most important factor affecting patient outcomes, so using a single team limits surgical bias. It also increased the credibility of the results.

Although we minimized bias to increase the accuracy of the results, clinical trials have limitations.[33] It was not possible to include all outcomes due to follow-up time constraints. There were also difficulties in applying the results of randomized trials to individual patients.

In conclusion, there is an emerging body of evidence that supports the use of HIPEC with CRS and systemic chemotherapy for recurrent EOC compared to CRS and chemotherapy alone. Our study aimed to evaluate the efficacy and safety of HIPEC in platinum-sensitive recurrent ovarian cancer patients with HRR mutations. Our results further support the role of HIPEC in patients with recurrent ovarian cancer and will help guide clinicians in the treatment of these patients.

Conclusion

We identified more effective and precise treatment modalities for EOC using a randomized controlled phase III clinical trial to evaluate the efficacy of HIPEC in patients with different HRR mutation status.

Author's Contribution

YQ, MD, and HC conceived and designed the study; YQ, YZ, and SY analyzed the results, YS, YQ, and MD contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Statement

Our study was approved by The Ethics Committee of the Zhongnan Hospital of Wuhan University (Approval No. 2020107, ethical approval date: May 18, 2020).

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