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TOPIC HIGHLIGHT

Federico Coccolini, MD, *Series Editor*

Criticalities in randomized controlled trials on HIPEC for ovarian cancer

Federico Coccolini, Luca Ansaloni, Davide Corbella, Marco Lotti, Olivier Glehen

Federico Coccolini, Luca Ansaloni, Marco Lotti, General Surgery Dept., Papa Giovanni XXIII Hospital, 24128 Bergamo, Italy
Davide Corbella, Department of Anesthesiology, Papa Giovanni XXIII Hospital, 24128 Bergamo, Italy
Olivier Glehen, Department of Surgical Oncology, Centre Hospitalier Lyon Sud, 69495 Pierre-Bénite, France
Author contributions: Coccolini F contributed to the study design, literature analysis and paper writing; Corbella D and Lotti M contributed to the literature research, literature analysis and manuscript approval; Ansaloni L and Glehen O contributed equally to the final manuscript editing and approval.
Correspondence to: Federico Coccolini, MD, General Surgery Dept., Papa Giovanni XXIII Hospital, P.zza OMS 1, 24128 Bergamo, Italy. federico.coccolini@gmail.com
Telephone: +39-35-2696464 Fax: +39-35-2674963
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Abstract

Since the 1990s, many oncological surgery groups around the world started to apply hyperthermic intraperitoneal chemotherapy (HIPEC) to the different peritoneal spread cancers. The rationale of the application of HIPEC after surgery is to complete the cytoreductive procedure. This combined treatment has now been successfully applied to many different intra-abdominal neoplasms. However, the treatment of peritoneal surface malignancies and the administration of HIPEC still lack high graded evidence data, especially in ovarian cancer. Experimental data exists about every step of the treatment of peritoneal spread ovarian cancer but unfortunately they have not yet been translated into phase Ⅲ clinical randomized trials. Moreover, treatment protocols differ between different centers. A systematic review of published randomized trial protocols was performed. HIPEC techniques are miscellaneous and not yet standardized. Well structured phase Ⅲ randomized trials among specialized centers are needed to investigate the efficacy of this therapeutic approach, as well as technical details that may contribute to the standardization of the procedure and limit morbidity and mortality. In particular, new criteria are mandatory to uniformly stage the disease, to objectively evaluate the extension of cytoreduction and consequently the residual disease, to decide the best method of performing hyperthermia and to perfuse drugs. Moreover, pharmacokinetic and pharmacodynamic studies are urgently needed to assess the best type and dose of anticancer drugs.

Key words: Randomized trial; Ovarian cancer; Hyperthermic intra-peritoneal chemotherapy; Hyperthermia

Core tip: Hyperthermic intra-peritoneal chemotherapy techniques are miscellaneous and not yet standardized. Well structured phase Ⅲ randomized trials among specialized centers are necessary to investigate the efficacy of this therapeutic approach, as well as technical details that may contribute to the standardization of the procedure and limit morbidity and mortality.

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INTRODUCTION

Treatment of peritoneal surface malignancies presents peculiar challenges to specialized teams who face them daily. The peritoneal spread of cancer, more than other forms of diffuse neoplastic disease, brings suffering to

patients directly linked to the loco-regional progression. These symptoms are often strongly disabling. Innovative therapies are developed day by day and applied to these cohorts of patients to control and/or palliate these symptoms that are often only due to the loco-regional cancer diffusion without systemic disease. In the 1980s, Sugarbaker *et al*[1] from the Washington Cancer Institute started to consider peritoneal carcinomatosis from intra-abdominal neoplasms as a loco-regional disease. They promoted a loco-regional treatment combining cytoreductive surgery (CRS) with intra-peritoneal (IP) administration of chemotherapy (CT). Adding hyperthermia to IP, CT was also investigated by Spratt *et al*[2] and has been successively performed and studied by many researchers and clinicians. Since the 1990s, many oncological surgery groups around the world started to apply hyperthermic intra-peritoneal chemotherapy (HIPEC) to the different peritoneal spread cancers[3]. The rationale of the application of HIPEC after CRS is to complete the cytoreduction by reaching all the microscopic cancer residuals which the surgeon cannot see and consequently remove. The combined treatment of CRS and HIPEC has now been successfully applied to many different intra-abdominal neoplasms[4-6]. Unfortunately, the peritoneal surface malignancies and the administration of HIPEC have always been based more on common sense than on high graded evidence data. Experimental data exists about every step of the treatment of IP cancers (CT, IP CT, CRS and HIPEC) but unfortunately they have not been translated into phase Ⅲ clinical randomized controlled trials (RCT) able to give high-impact results to demonstrate the real impact of HIPEC on the clinical course of IP cancers, especially of advanced epithelial ovarian cancer (EOC)[7].

RESEARCH STRATEGY

A thorough literature search of MEDLINE, EMBASE, COCHRANE, ClinicalTrial.gov, WHO International Clinical Trials Registry Platform and the EU Clinical Trials Register electronic databases was performed by 2 independent reviewers (FC and DC) to identify relevant studies. Bibliography evaluation of all selected study and recent reviews was performed to identify all additional studies. The search was not limited to any time duration. Only papers written in English were considered. To enable assimilation of all relevant published research, all search terms were expanded and all sub-categories were included. The exact syntax of search terms included ovarian neoplasms as well as randomized trial and other mesh terms.

SELECTION CRITERIA

Inclusion into the current systematic review was based on the following criteria for all retrieved studies: randomized trials evaluating the use of HIPEC in ovarian cancer. The purpose is to analyse discrepancies between the different protocols by studying the same disease in terms of inclusion/exclusion criteria, duration and kind of therapy, follow-up and primary and secondary outcomes.

IDENTIFIED STUDIES

A search of the databases using the above search terms led to identification of a total of 7 papers, five published protocols and 2 proposed studies. The complete manuscripts of all 5 published protocols were independently assessed and included in the review.

DATA EXTRACTION

Information from the studies was extracted by 2 researchers (FC and DC) using the data extraction form. Disagreements about data analysis were solved by discussion with a third author (ML).

Seven RCTs evaluating the effectiveness of HIPEC in EOC at different time points of EOC evolution have been proposed; five are already on course (Table 1)[8-11] and two have been only proposed[12].

The first is a South Korean study (NCT01091636)[9]. It is a phase Ⅱ trial evaluating the efficacy of HIPEC in the treatment of either primary or recurrent ovarian cancer. All patients in this trial will be scheduled to undergo CRS. After surgery, if the residual disease is less than 1 cm in the recurrent disease group, patients will always receive HIPEC. In the primary disease group, patients are randomized to receive HIPEC or not. Primary endpoint is progression free survival; secondary end points are overall survival and quality of life. The sample size is 168 patients and the completion date will be December 2013. HIPEC will be performed at a mean temperature of 41.5 ℃ for 90 min with platinum at a dose of 75 mg/m^2. This study enrols participants only by invitation.

The second is a study from the Netherlands (NCT00426257)[9]. It is a phase Ⅲ trial evaluating the efficacy of HIPEC after secondary debulking surgery. The scheduled 280 patients will be randomized to receive secondary debulking surgery with or without HIPEC. The two criteria indicated as indication for secondary debulking are the impossibility of performing primary debulking for tumor extension or the patient's general condition or a primary debulking procedure with a residual disease of more than 1 cm. In both cases, patients will undergo chemotherapy before the surgical procedure. Primary outcome is recurrent free survival; secondary outcomes are toxicity, morbidity, quality of life, tumor response and overall survival. The finishing date will be March 2013. HIPEC will be performed with platinum at a dose of 100 mg/m^2.

The last published protocol evaluating HIPEC in primary advanced EOC (NCT01628380)[8] is the CHORINE study. This is an Italian multicentric trial which has the peculiar characteristic of evaluating the role of HIPEC after neo-adjuvant chemotherapy. This phase Ⅲ trial is scheduled to recruit 94 patients to be randomized into two arms. The randomization will be done after

Table 1 Studies included in the review

Protocol no. (Name)	Country	Time point	Sample size	Randomization	Treatments	Primary outcome	Secondary outcome
NCT01091636	South Korea	Primary, recurrent OC	168	After surgery residual disease < 1 cm	CRS ± HIPEC with platinum 75 mg/m^2 at 41.5 ℃ for 90 min	Progression free survival	Overall survival, quality of life
NCT00426257	The Netherlands	Secondary debulking surgery	280	ND	CRS ± HIPEC with platinum 100 mg/m^2	Recurrence free survival	Toxicity, morbidity, quality of life, tumor response and overall survival
NCT01628380 (CHORINE study)	Italy	Primary advanced OC after NACT	94	After surgery residual disease < 2.5 mm	CRS ± HIPEC with platinum 100 mg/m^2 + taxol 175 mg/m^2, at 42 ℃ for 90 min, open or closed technique	Disease free survival	Morbidity, mortality, time to chemotherapy beginning after surgery, overall survival, 1, 3, 5-yr disease free survival and 1, 3, 5-yr overall survival
NCT01376752 (CHIPOR study)	France	Recurrent OC	444	After surgery residual disease < 2.5 mm	CRS ± HIPEC platinum 75 mg/m^2	Overall survival	Relapse free survival
NCT01539785 (HORSE study)	Italy	Recurrent OC	158	ND	CRS ± HIPEC platinum 75 mg/m^2) at 41.5 ℃ for 60 min, closed technique	Progression free interval	Overall survival, morbidity and mortality

OC: Ovarian cancer; NACT: Neoadjuvant chemotherapy; HIPEC: Hyperthermic intraperitoneal chemotherapy; CRS: Cytoreductive surgery; ND: Not declared.

CRS. Only patients with an optimal completeness of cytoreduction with a residual disease of a maximum of 2.5 mm will be randomized. The primary outcome will be the disease free survival and the secondary ones will be morbidity, mortality, time to chemotherapy beginning after surgery, overall survival, 1, 3, 5-year disease free survival and 1, 3, 5-year overall survival. Platinum (100 mg/m^2) plus taxol (175 mg/m^2) will be administered with either an open or closed technique at a temperature of 42 ℃ for 90 min for HIPEC. The scheduled finishing date will be June 2014.

Two randomized trials evaluate the efficacy in recurrent EOC. The first is the CHIPOR study (NCT01376752)[10]. This multicentric phase Ⅲ trial from France aims to study the effect of HIPEC on complete cytoreduced patients (CC-0 or CC-1 with a residual of max 0.25 cm). The randomization will be done after cytoreduction. If CC-0 or CC-1 criteria are reached, patients will undergo HIPEC with platinum at 75 mg/m^2. Primary outcome is overall survival and the secondary outcome is relapse free survival. The scheduled number of patients is 444 and the scheduled finishing date is April 2018.

The last registered trial is the HORSE study (NCT01539785)[11]. This Italian multicentric phase Ⅲ trial randomizes patients into two arms and CRS will be compared to CRS + HIPEC. The CRS + HIPEC arm patients will be treated with platinum (75 mg/m^2) at 41.5 ℃ for 60 min with a closed technique. Primary outcome is progression free interval and the secondary outcomes are overall survival, morbidity and mortality. The scheduled number of patients to be enrolled is 158 and the scheduled finishing date is February 2015.

Lastly, two proposed trials have to be mentioned. These two proposals have been published in a letter by Chua *et al*[11]. The authors proposed two trials to investigate the HIPEC procedure in primary and advanced ovarian cancer, dividing patients into two arms for each study and treating them with either CRS plus HIPEC (platinum 100 mg/m^2) or CRS alone. In their opinion, the CRS effort should be maximal and its aim is the absence of macroscopic residual disease.

As already stressed by other authors[12-14], the main difficulty to reach clinically relevant results in the treatment of EOC with HIPEC is strongly determined by the impossibility of obtaining a sufficient number of patients in a single center. In fact, in many centers, patients with peritoneal carcinomatosis are still considered as terminal and so are often not referred to the specialized surgical oncology groups to be correctly evaluated. Many clinicians are sceptical about the use of such an aggressive regimen of CRS plus HIPEC because of the potential increase in morbidity and mortality in a category of weak patients. Also, patients challenge the accrual for RCT because their referral to peritoneal surface malignancies specialized centers is mainly driven by the will to undergo CRS and HIPEC. They seldom accept to be randomized to receive HIPEC treatment or not. Lastly, the single institution is an obstacle that strongly limits the possibility of participating in a multicenter RCT. Each center in fact utilizes different procedures, surgeons operate in a different way and consider the completeness of cytoreduction differently at any time point[15,16], and anesthesiologists or surgeons adopt different pre- and post-operative care systems.

RCTs about HIPEC are poorly or not sponsored by pharmaceutical companies which prefer to promote trials where chemotherapy is administered systemically with new targeted agents[17]. Moreover, the different studies are mainly retro- or prospective phase Ⅰ and Ⅱ; insuffi-

cient randomized phase Ⅲ trials exist. Standard treatment has to be inserted into these kinds of trials with an arm to compare, which allows discerning the real impact of HIPEC without a confounding bias. On the other hand, however, the possibility of concluding a multicentric randomized trial crashes against the different habits or institutional lacking, which increases the difficulty of getting homogeneous proceedings in the different centers. To all these factors has to be added the lack of scientifically defined indications about the chemotherapy regimens. Intraperitoneal chemotherapy in fact is often administered at a "common sense dose". Each center adopts a different dosage determined either by the patient characteristics or the habits or personal belief of the operators. No definitive studies exist about the drug dosages to be used intraperitoneally. No studies have in fact evaluated the optimal dose in relationship to the efficacy, tissue penetration and cancer penetration in big samples of population because the necessary sample size would be huge. However, we are studying the efficacy of HIPEC without knowing how its administration is done. From the surgical point of view, in fact, technical improvement has nearly reached its maximum. We certainly need to know if and how HIPEC allows gain in DFS or OS. However, we still do not know if and how we can gain improvement with chemotherapy with the commonly used drugs.

Another issue to be clarified is the duration of perfusion. No definitive pharmacokinetic and pharmacodynamic studies have clarified the right time, right doses or the administration interval for the different drugs. Some authors perfuse for 60 min; others for 90 min. Some administer all drugs at the beginning; other fractionate the doses into 2, 3 or more administrations, in consideration of the kinetics of the molecules.

Some authors utilize the open technique; others the closed one. Experimental studies demonstrated the different drug distribution in the different techniques. However, no definitive data and consequently indication have been published.

Complications of the procedure are reported using many different reporting scales. Each scale differentiates complications in its own manner and no conclusive data could be obtained[4]. Some authors classified complications and adverse events by using the Bozzetti classification[18]. Others authors have used different classification systems, such as the Clavien one or its two proposed modifications from Feldman or Elias[15]. Others have used the National Institute of Health Common Terminology Criteria for Adverse Events (CTCAE)[18]. These scales are not specifically designed to assess and report CRS + HIPEC complications. The 2006 peritoneal surface malignancies workshop (Milan, Italy) established the CTCAE as the standard system to report CRS+HIPEC complications. However, no univocal classification has been adopted yet. For this reason, no comparison between the different reports could be done.

In the majority of studies dedicated to therapeutic strategy in ovarian cancer, no information is reported regarding peritoneal disease extent as the FIGO classification is used. Stage Ⅲc includes patients with localized disease and patients with extensive peritoneal carcinomatosis. When classification of the disease distribution is reported, two main grading systems are used. The Gilly classification partially considers dimension or diffusion but gives an incomplete idea of the surgical field before CRS[19]. The peritoneal cancer index (PCI) by Sugarbaker and Jacquet precisely described dimension or distribution of the disease[20]. This allows uniform data and results. Moreover, PCI was demonstrated to have prognostic value[21,22].

The classification of the completeness of cytoreduction is still controversial. Different scoring systems are used; mainly the Lyon[23] and the Sugarbaker classification[17]. The increase in DFS benefit with the increasing of the completeness of cytoreduction toward no residual disease[4,24,25] is demonstrated. The scientific community is modifying its opinion by agreeing on the meaning of complete cytoreduction as no macroscopic residual disease. However, there is no univocal opinion and consequently the surgical goal still has to be reached in this field.

CONCLUSION

HIPEC techniques are miscellaneous and not yet standardized. Well structured phase Ⅲ randomized trials among specialized centers are necessary to investigate the efficacy of this therapeutic approach, as well as technical details that may contribute to the standardization of the procedure and limit morbidity and mortality. In particular, new criteria are mandatory to uniformly stage the disease, to objectively evaluate the extension of cytoreduction and consequently the residual disease, to decide the best method to perform hyperthermia and to perfuse drugs. Moreover pharmacokinetic and pharmacodynamic studies are urgently needed to assess the best type and dose of anticancer drugs.

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