World Journal of Obstetrics and Gynecology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5317/wjog.v4.i3.64

World J Obstet Gynecol 2015 August 10; 4(3): 64-67
ISSN 2218-6220 (online)

EDITORIAL

Value of neoadjuvant chemotherapy in advanced ovarian cancer

Federico Coccolini, Fausto Catena, Roberto Manfredi, Giulia Montori, Jennifer E Manegold, Luca Ansaloni

Federico Coccolini, Roberto Manfredi, Giulia Montori, Luca Ansaloni, General and Emergency Surgery Department, Papa Giovanni XXIII Hospital, 24128 Bergamo, Italy

Fausto Catena, Emergency Surgery Department, Ospedale Maggiore, 43100 Parma, Italy

Jennifer E Manegold, David Geffen School of Medicine, University of California, Los Angeles, CA 90073, United States

Author contributions: Coccolini F, Catena F and Ansaloni L analyzed data, drafted the manuscript and gave final approval; Manfredi R, Montori G and Manegold JE critically revised the manuscript, gave final approval.

Conflict-of-interest statement: All authors declare to have no conflict of interest.

Correspondence to: Federico Coccolini, MD, General and Emergency Surgery Department, Papa Giovanni XXIII Hospital, P.zza OMS 1, 24128 Bergamo, Italy. federico.coccolini@gmail.com
Telephone: +39-35-2673486
Fax: +39-35-2674963

Received: February 10, 2015
Peer-review started: February 13, 2015
First decision: March 6, 2015
Revised: March 20, 2015
Accepted: June 18, 2015
Article in press: June 19, 2015
Published online: August 10, 2015

Abstract

Data regarding the role of neoadjuvant chemotherapy (NACT) are not definitive. Several randomized trials and meta-analyses demonstrate that this chemotherapy regimen decreases the morbidity and mortality rates and increases complete cytoreduction rates. If combined with hyperthermic intraperitoneal chemotherapy (HIPEC), NACT could potentially further improve upon these already promising results. Moreover the use of NACT could help in evaluating the chemo-sensitivity of the cancer, thus preventing unnecessary HIPEC procedures in chemo-resistant patients. NACT should definitely be considered as a preferred regimen in the management of advanced ovarian cancer, especially in association with cytoreductive surgery + HIPEC procedure in the context of a multidisciplinary team management in an experienced cancer centre.

Key words: Epithelial ovarian cancer; Neoadjuvant; Chemotherapy; Hyperthermic intraperitoneal chemotherapy; Treatment; Oncology; Cytoreductive surgery

Core tip: Data about the use of neoadjuvant chemotherapy in advanced ovarian cancer are not sufficient to support its extensive application. However encouraging results came from the existing studies. Future well designed studies are needed to clarify some aspects of this chemotherapy regimen and its association with the other form of pharmacological and surgical therapy.

Coccolini F, Catena F, Manfredi R, Montori G, Manegold JE, Ansaloni L. Value of neoadjuvant chemotherapy in advanced ovarian cancer. *World J Obstet Gynecol* 2015; 4(3): 64-67 Available from: URL: http://www.wjgnet.com/2218-6220/full/v4/i3/64.htm DOI: http://dx.doi.org/10.5317/wjog.v4.i3.64

INTRODUCTION

One of the most common malignancies and one of

the principal causes of death among gynaecological neoplasm is epithelial ovarian cancer (EOC)[1]. The majority of EOC patients (about 70%) present with an advanced FIGO (International Federation of Gynecology and Obstetrics) stage disease (III or IV)[2-5]. Currently the standard treatment for these patients consists of complete cytoreduction (CC) followed by combined systemic chemotherapy of a platinum agent and paclitaxel[1,6]. Optimal cytoreduction was found to be one of the strongest survival determinants among patients with advanced stage[7-12].

NACT AND INTERVAL DEBULKING SURGERY

Recently, interval-debulking-surgery (IDS) after a short course of neoadjuvant chemotherapy (NACT), usually three cycles, has been demonstrated to be a viable alternative in those patients with low probability to obtain a CC during primary debulking surgery (PDS)[13]. Three randomized controlled trials (RCT) have demonstrated that overall survival (OS) and progression-free survival (PFS) in patients who received NACT plus IDS were not different from patients who received PDS. However, patients who received NACT had significantly lower adverse events and lower mortality after IDS than after PDS[14-16].

The first RCT, by the European Organization for the Research and Treatment of Cancer (EORTC) evaluated the benefit of IDS after suboptimal PDS. One-hundred and forty patients treated with three cycles of cisplatin and cyclophosphamide chemotherapy followed by IDS plus three cycles of ACT were compared with 138 similar patients receiving the same chemotherapy regimen without IDS. Data obtained from this study showed that patients from the IDS group had a median survival time statistically significant longer (26 mo) than patients not treated with IDS (20 mo)[14].

The second RCT conducted by the Gynecologic Oncology Group, evaluated 550 patients (stage III-IV) with a residual disease > 1 cm after PDS[15]. All patients received three cycles of initial chemotherapy with cisplatin and paclitaxel followed by response evaluation. Patients with no disease progression were randomized to IDS plus three additional cycles of ACT or additional chemotherapy alone. No differences between the two groups were found with regard to PFS or OS[15].

The third RCT performed by EORTC with the National Cancer Institute of Canada (NCIC) compared PDS with NACT plus IDS[16]. Seven hundreds and eighteen patients with EOC, fallopian tube or primary peritoneal carcinoma were included. All patients had stage IIIC-IV disease and were randomized to PDS plus platinum chemotherapy or NACT plus IDS. The CC was optimal (residual disease $\leqslant$ 1 cm) in 41.6% of patients after PDS and in 80.6% after IDS. PFS and OS were similar in both groups. Postoperative complications and postoperative mortality were higher after PDS[16].

A meta-analysis from Bristow *et al*[17] showed poor results for NACT used instead of PDS in advanced EOC. However this meta-analysis also demonstrated increased survival with an easier IDS prior to NACT and decreased survival with increasing number of chemotherapy cycles prior to IDS. Chua *et al*[18] suggested that the treatment of advanced EOC should primarily involve a massive surgical effort for CC, and NACT may be considered when the extent of the disease decreases the possibility of achieving a CC[1]. Another meta-analysis by Kang and Nam[19] showed a positive correlation between use of NACT and increased rate of CC in patients at high risk for suboptimal debulking and/or unfavourable general conditions.

Tangjitgamol *et al*[20] stated in a third meta-analysis that no conclusive evidence could be obtained to determine whether NACT increased or decreased survival rate.

NACT AND CRS PLUS HIPEC

Extensive data from the last ten years demonstrate that improved long-term results can be achieved in select patients using cytoreductive surgery (CRS), including parietal and visceral peritonectomy procedures, in combination with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC)[18,21-30].

Data from the literature are encouraging though not entirely homogeneous[31]. Nevertheless, as stated by Markman[32], the absence of phase-III trials suggests a few considerations before definitively validating CRS plus HIPEC as a viable strategy for first-line treatment of advanced EOC[1].

While the majority of patients with EOC (up to 80%) respond to the first-line platinum based chemotherapy, almost 20% of patients are resistant or refractory[1,33]. The greatest risk is for patients requiring CRS plus HIPEC[1]. CC is associated with high postoperative morbidity and mortality rates especially in advanced cases[9,34,35]. This could potentially be increased by HIPEC as it remains a burdensome procedure. For this reason, the goal would be to select patients suitable to achieve the maximum benefit and to reduce the need for surgical resections[1]. Even if NACT followed by CRS plus HIPEC does not show better results in terms of PFS and OS[16,36], the evaluation of the NACT response may help in selecting for HIPEC-only patients who demonstrate chemo-sensitivity. In fact, NACT could have the additional benefit of providing the "*ex-iuvantibus*" chemo-sensitivity determination[1]. HIPEC with platinum compounds and taxanes in fact has been demonstrated as feasible and safe[30,37].

The addition of NACT to the current treatment regimen as documented in the literature provides some advantages with regards to morbidity reduction and completeness of cytoreduction, especially in preoperatively well-staged patients. As CC is one of the strongest predictors of survival, it is not yet well-understood why studies have failed to show an improvement in OS or DFS with NACT[7]. Nevertheless,

NACT shows great promise in its potential to prevent unnecessary use of HIPEC and to reduce surgical load, thus decreasing post-operative morbidity and mortality.

CONCLUSION

The use of NACT in the treatment of advanced EOC is progressively increasing. Studies about its use in several setting are on-going. This chemotherapy regimen should be considered as a preferred regimen in the management of advanced EOC, especially when combined with CRS plus HIPEC procedure in the context of a multidisciplinary team management in an experienced cancer centre. Results from the on-going RCT will clarify several issues about the association and the real survival effects of NACT associated to CRS plus HIPEC. Future well-designed studies are needed to clarify some aspects of this chemotherapy regimen and its association with the other form of pharmacological and surgical therapy.

REFERENCES

1 **Coccolini F**, Catena F, Manfredi R, Lotti M, Frigerio L, Ansaloni L. Advanced ovarian cancer: neoadjuvant chemotherapy plus surgery and HIPEC as up-front treatment. *World J Obstet Gynecol* 2012; **1**: 55-59 [DOI: 10.5317/wjog.v1.i4.55]

2 **Bonnefoi H**, A'Hern RP, Fisher C, Macfarlane V, Barton D, Blake P, Shepherd JH, Gore ME. Natural history of stage IV epithelial ovarian cancer. *J Clin Oncol* 1999; **17**: 767-775 [PMID: 10071265]

3 **Yancik R**. Ovarian cancer. Age contrasts in incidence, histology, disease stage at diagnosis, and mortality. *Cancer* 1993; **71**: 517-523 [PMID: 8420671 DOI: 10.1002/cncr.2820710205]

4 **Cannistra SA**. Cancer of the ovary. *N Engl J Med* 2004; **351**: 2519-2529 [PMID: 15590954 DOI: 10.1056/NEJMra041842]

5 **Karlan BY**, Markman MA, Eifel PJ. Ovarian cancer, peritonealcarcinoma and fallopian tube carcinoma. In: DeVita VT Jr, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 7th ed. Williams and Wilkins, Lippincott, 2005: 1364-1397

6 **Abu-Rustum NR**, Chi DS, Curtin JP. Epithelial ovarian cancer. *Curr Probl Surg* 1999; **36**: 1-53 [PMID: 9924485 DOI: 10.1016/S0011-3840(99)80005-7]

7 **Bristow RE**, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* 2002; **20**: 1248-1259 [PMID: 11870167 DOI: 10.1200/JCO.20.5.1248]

8 **Hoskins WJ**, McGuire WP, Brady MF, Homesley HD, Creasman WT, Berman M, Ball H, Berek JS. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am J Obstet Gynecol* 1994; **170**: 974-979; discussion 979-980 [PMID: 8166218 DOI: 10.1016/S0002-9378(94)70090-7]

9 **Hoskins WJ**, Bundy BN, Thigpen JT, Omura GA. The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume stage III epithelial ovarian cancer: a Gynecologic Oncology Group study. *Gynecol Oncol* 1992; **47**: 159-166 [PMID: 1468693 DOI: 10.1016/0090-8258(92)90100-W]

10 **Frigerio L**, Ansaloni L, Poiasina E, Coccolini F, Sugarbaker PH. Comprehensive management of epithelial ovarian cancer with peritoneal metastases. *World J Obstet Gynecol* 2013; **2**: 108-115 [DOI: 10.5317/wjog.v2.i4.108]

11 **Ansaloni L**, Coccolini F, Catena F, Frigerio L, Bristow R. Cytoreductive surgery in primary advanced EOC. *World J Obstet Gynecol* 2013; **2**: 116-123 [DOI: 10.5317/wjog.v2.i4.116]

12 **Eskander R**, Ansaloni L, Bristow R, Coccolini F. Cytoreductive surgery and HIPEC in epithelian ovarian cancer: state of the art. *World J Obstet Gynecol* 2013; **2**: 94-100 [DOI: 10.5317/wjog.v2.i4.94]

13 **Sato S**, Itamochi H. Neoadjuvant chemotherapy in advanced ovarian cancer: latest results and place in therapy. *Ther Adv Med Oncol* 2014; **6**: 293-304 [PMID: 25364394 DOI: 10.1177/1758834014544891]

14 **van der Burg ME**, van Lent M, Buyse M, Kobierska A, Colombo N, Favalli G, Lacave AJ, Nardi M, Renard J, Pecorelli S. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 1995; **332**: 629-634 [PMID: 7845426 DOI: 10.1056/NEJM199503093321002]

15 **Rose PG**, Nerenstone S, Brady MF, Clarke-Pearson D, Olt G, Rubin SC, Moore DH, Small JM. Secondary surgical cytoreduction for advanced ovarian carcinoma. *N Engl J Med* 2004; **351**: 2489-2497 [PMID: 15590951 DOI: 10.1056/NEJMoa041125]

16 **Vergote I**, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, Verheijen RH, van der Burg ME, Lacave AJ, Panici PB, Kenter GG, Casado A, Mendiola C, Coens C, Verleye L, Stuart GC, Pecorelli S, Reed NS. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med* 2010; **363**: 943-953 [PMID: 20818904 DOI: 10.1056/NEJMoa0908806]

17 **Bristow RE**, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. *Gynecol Oncol* 2009; **112**: 265-274 [PMID: 18937969 DOI: 10.1016/j.ygyno.2008.08.033]

18 **Chua TC**, Robertson G, Liauw W, Farrell R, Yan TD, Morris DL. Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery in ovarian cancer peritoneal carcinomatosis: systematic review of current results. *J Cancer Res Clin Oncol* 2009; **135**: 1637-1645 [PMID: 19701772 DOI: 10.1007/s00432-009-0667-4]

19 **Kang S**, Nam BH. Does neoadjuvant chemotherapy increase optimal cytoreduction rate in advanced ovarian cancer? Meta-analysis of 21 studies. *Ann Surg Oncol* 2009; **16**: 2315-2320 [PMID: 19517192 DOI: 10.1245/s10434-009-0558-6]

20 **Tangjitgamol S**, Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A. Interval debulking surgery for advanced epithelial ovarian cancer. *Cochrane Database Syst Rev* 2010; **(10)**: CD006014 [PMID: 20927744 DOI: 10.1002/14651858.CD006014.pub5]

21 **Kecmanovic DM**, Pavlov MJ, Kovacevic PA, Ceranic MS, Stamenkovic AB. Cytoreductive surgery for ovarian cancer. *Eur J Surg Oncol* 2003; **29**: 315-320 [PMID: 12711282 DOI: 10.1053/ejso.2002.1367]

22 **Deraco M**, Rossi CR, Pennacchioli E, Guadagni S, Somers DC, Santoro N, Raspagliesi F, Kusamura S, Vaglini M. Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion in the treatment of recurrent epithelial ovarian cancer: a phase II clinical study. *Tumori* 2001; **87**: 120-126 [PMID: 11504363]

23 **Look M**, Chang D, Sugarbaker PH. Long-term results of cytoreductive surgery for advanced and recurrent epithelial ovarian cancers and papillary serous carcinoma of the peritoneum. *Int J Gynecol Cancer* 2003; **13**: 764-770 [PMID: 14675312 DOI: 10.1111/j.1525-1438.2003.13319.x]

24 **Helm CW**, Randall-Whitis L, Martin RS, Metzinger DS, Gordinier ME, Parker LP, Edwards RP. Hyperthermic intraperitoneal chemotherapy in conjunction with surgery for the treatment of recurrent ovarian carcinoma. *Gynecol Oncol* 2007; **105**: 90-96 [PMID: 17173957 DOI: 10.1016/j.ygyno.2006.10.051]

25 **Cotte E**, Glehen O, Mohamed F, Lamy F, Falandry C, Golfier F, Gilly FN. Cytoreductive surgery and intraperitoneal chemo-hyperthermia for chemo-resistant and recurrent advanced epithelial ovarian cancer: prospective study of 81 patients. *World J Surg* 2007; **31**: 1813-1820 [PMID: 17629740 DOI: 10.1007/s00268-007-9146-8]

26 **Gori J**, Castaño R, Toziano M, Häbich D, Staringer J, De Quirós DG, Felci N. Intraperitoneal hyperthermic chemotherapy in ovarian cancer. *Int J Gynecol Cancer* 2005; **15**: 233-239 [PMID: 15823105 DOI: 10.1111/j.1525-1438.2005.15209.x]

27 **Roviello F**, Pinto E, Corso G, Pedrazzani C, Caruso S, Filippeschi M, Petrioli R, Marsili S, Mazzei MA, Marrelli D. Safety and potential benefit of hyperthermic intraperitoneal chemotherapy (HIPEC) in peritoneal carcinomatosis from primary or recurrent ovarian cancer. *J Surg Oncol* 2010; **102**: 663-670 [PMID: 20721959 DOI: 10.1002/jso.21682]

28 **Ansaloni L**, Agnoletti V, Amadori A, Catena F, Cavaliere D, Coccolini F, De Iaco P, Di Battista M, Framarini M, Gazzotti F, Ghermandi C, Kopf B, Saponara M, Tauceri F, Vallicelli C, Verdecchia GM, Pinna AD. Evaluation of extensive cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with advanced epithelial ovarian cancer. *Int J Gynecol Cancer* 2012; **22**: 778-785 [PMID: 22572845 DOI: 10.1097/IGC.0b013e31824d836c]

29 **Coccolini F**, Gheza F, Lotti M, Virzì S, Iusco D, Ghermandi C, Melotti R, Baiocchi G, Giulini SM, Ansaloni L, Catena F. Peritoneal carcinomatosis. *World J Gastroenterol* 2013; **19**: 6979-6994 [PMID: 24222942 DOI: 10.3748/wjg.v19.i41.6979]

30 **Coccolini F**, Campanati L, Catena F, Ceni V, Ceresoli M, Jimenez Cruz J, Lotti M, Magnone S, Napoli J, Rossetti D, De Iaco P, Frigerio L, Pinna A, Runnebaum I, Ansaloni L. Hyperthermic intraperitoneal chemotherapy with cisplatin and paclitaxel in advanced ovarian cancer: a multicenter prospective observational study. *J Gynecol Oncol* 2015; **26**: 54-61 [PMID: 25376916 DOI: 10.3802/jgo.2015.26.1.54]

31 **Coccolini F**, Ansaloni L, Corbella D, Lotti M, Glehen O. Criticalities in randomized controlled trials on HIPEC for ovarian cancer. *World J Obstet Gynecol* 2013; **2**: 124-128 [DOI: 10.5317/wjog.v2.i4.124]

32 **Markman M**. Platinum-based neoadjuvant chemotherapy for advanced ovarian cancer. *Gynecol Oncol* 2007; **106**: 273-274; author reply 274-275 [PMID: 17467780 DOI: 10.1016/j.ygyno.2007.03.013]

33 **Leitao MM**, Chi DS. Surgical management of recurrent ovarian cancer. *Semin Oncol* 2009; **36**: 106-111 [PMID: 19332245 DOI: 10.1053/j.seminoncol.2008.12.002]

34 **Gerestein CG**, Nieuwenhuyzen-de Boer GM, Eijkemans MJ, Kooi GS, Burger CW. Prediction of 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer. *Eur J Cancer* 2010; **46**: 102-109 [PMID: 19900801 DOI: 10.1016/j.ejca.2009.10.017]

35 **Gerestein CG**, Damhuis RA, Burger CW, Kooi GS. Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: a systematic review. *Gynecol Oncol* 2009; **114**: 523-527 [PMID: 19344936 DOI: 10.1016/j.ygyno.2009.03.011]

36 **Vergote I**, Amant F, Kristensen G, Ehlen T, Reed NS, Casado A. Primary surgery or neoadjuvant chemotherapy followed by interval debulking surgery in advanced ovarian cancer. *Eur J Cancer* 2011; **47** Suppl 3: S88-S92 [PMID: 21944035 DOI: 10.1016/S0959-8049(11)70152-6]

37 **Ansaloni L**, Coccolini F, Morosi L, Ballerini A, Ceresoli M, Grosso G, Bertoli P, Busci LM, Lotti M, Cambria F, Pisano M, Rossetti D, Frigerio L, D'Incalci M, Zucchetti M. Pharmacokinetics of concomitant cisplatin and paclitaxel administered by hyperthermic intraperitoneal chemotherapy to patients with peritoneal carcinomatosis from epithelial ovarian cancer. *Br J Cancer* 2015; **112**: 306-312 [PMID: 25461804 DOI: 10.1038/bjc.2014.602]

P- Reviewer: Khajehei M, Tsikouras P, Yokoyama Y
S- Editor: Song XX **L- Editor**: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com