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REVIEW

Advanced ovarian cancer: Neoadjuvant chemotherapy plus surgery and HIPEC as up-front treatment

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Abstract

Epithelial ovarian cancer (EOC) is one of the most common malignancies and one of the principal causes of death in gynecological neoplasms. The majority of EOC patients present with an advanced International Federation of Gynecology and Obstetrics stage disease. The current standard treatment for these patients consists of complete cytoreduction and combined systemic chemotherapy of a platinum agent and paclitaxel. Even if the majority of patients with EOC respond to first-line platinum based chemotherapy, almost 20% of them are resistant or refractory. According to these data, the main risk is for a certain number of patients to have undergone cytoreductive surgery (CRS) and subsequent hyperthermic intraoperative peritoneal chemotherapy (HIPEC) in a useful way. Radical surgery, especially in advanced cases, is associated with a high incidence of postoperative morbidity and mortality, which could be increased by the HIPEC. Every effort should be made for previously selected patients to improve outcome and optimize resources. Over the last decade, new options have been introduced to prolong survival. Improved long-term results can be achieved using CRS in combination with intraoperative HIPEC. This combination has also been used in an up-front setting. Controversial outcomes have been reported for neoadjuvant platinum-based chemotherapy. Different papers have been published reporting discordant results. Further studies are needed.

Key words: Epithelian ovarian cancer; Hyperthermic intraoperative peritoneal chemotherapy; Up-front; Neoadjuvant; Treatment; Oncology; Cytoreductive surgery; Chemotherapy

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EDITORIAL

Epithelial ovarian cancer (EOC) is one of the most common malignancies and one of the principal causes of death in gynecological neoplasms. The majority of EOC patients (about 70%) present with an advanced International Federation of Gynecology and Obstetrics (FIGO) stage disease (i.e., Ⅲ or Ⅳ)[1-4]. The current standard treatment for these patients consists of complete cytoreduction and combined systemic chemotherapy of a platinum agent and paclitaxel[5]. The extent of cytoreduction has a direct impact on survival and maximal cytoreduc-

tion was found to be one of the most powerful determinants of survival among patients with stage Ⅲ or Ⅳ EOC in a meta-analysis of almost 7000 patients[6] and in other studies[7-8]. The aim of cytoreductive surgery (CRS) is to remove all the macroscopic disease. Optimal cytoreduction is usually defined as a residual disease of less than 0.5-2 cm. However, it has been demonstrated that the achievement of an optimal cytoreduction, mainly in advanced EOC, is not always possible. Factors which mainly influence suboptimal cytoreduction are: the extent of the disease at the presentation, medical co-morbidities and the surgeon's expertise[9-11]. Sub-optimal and incomplete CRS results in losing the chance to improve survival. In our opinion, however, optimal cytoreduction should no longer be defined as a variable (0.5-2 cm) residual tumor but should be started to be considered as the complete absence of macroscopic residual disease. For this reason, patients should receive treatment only at centers able to undertake complex cytoreductive procedures[12]. Furthermore, phase Ⅲ randomised controlled trials have established the superiority [i.e., improved progression-free survival (PFS) and overall survival (OS) rates] of intraperitoneal cisplatin-based chemotherapy compared to the systemic delivery of the agent for the treatment of small-volume residual advanced EOC[13-15]. Less evidence is available for either medical[16] or surgical[17,18] management of recurrent EOC. Over the last decade, new options have been introduced to prolong survival.

A meta-analysis from Bristow *et al*[18] demonstrated poor outcomes for using neoadjuvant platinum-based chemotherapy instead of primary surgery in advanced EOC. However, this meta-analysis also demonstrated the increase of survival with debulking surgery with a better interval and the negative survival effect of increasing the number of chemotherapy cycles prior to interval surgery. Chua *et al*[19] suggested that the treatment of this malignancy should primarily involve a massive surgical effort for complete cytoreduction and neo-adjuvant chemotherapy (NAC) may be considered in situations where the extension of the disease provokes big limitations to the possibility of achieving a complete cytoreduction[19]. They also excluded the possibility of using the NAC to select a favourable prognostic group of chemo-responsive patients to undergo aggressive surgical cytoreduction[19]. Another meta-analysis by Kang and Nam[20] stated that NAC helps to obtain an increased rate of optimal cytoreduction in patients at a high risk for suboptimal debulking and/or unfavorable general conditions. However, it is not likely that the increased optimal debulking rate with NAC will result in improved survival outcome of patients with advanced EOC. The last meta-analysis by Tangjitgamol stated that no conclusive evidence could be obtained to determine whether NAC would improve or decrease survival rate[9].

A randomized trial comparing primary debulking surgery with NAC in EOC showed that similar OS and PFS may be achieved compared to standard primary debulking and with lower complication and post-operative mortality rate[21,22].

Improved long-term results can be achieved in highly selected patients using CRS, including parietal and visceral peritonectomy procedures, in combination with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC)[23-31]. Recent data from a multi-center phase Ⅱ trial using CRS and HIPEC with cisplatin and doxorubicin in up-front treatment of EOC reported good results[31]. The authors accrued 26 patients over 6 years in 4 different centers, achieving macroscopically complete cytoreduction in 15 patients and only minimal residual disease ($\leqslant$ 2.5 mm) in the remaining 11. Although major complications occurred in four patients, including one postoperative death, 25 of the 26 patients started systemic chemotherapy within a median of 46 d after surgery. A five year OS of 60.7% and a PFS of 15.2% were obtained. Another pilot experience reported good results in using CRS + HIPEC in an up-front setting[30,32]. Literature results are encouraging. In any case, as stated by different authors[18,33], the absence of phase-Ⅲ trials suggests a few considerations before validating CRS + HIPEC as a strategy for up-front treatment of advanced EOC.

Even if the majority of patients with EOC (up to 80%) respond to the first-line platinum based chemotherapy, almost 20% of them are resistant or refractory[17]. According to these data, the main risk is for a certain number of patients to have undergone CRS and subsequent HIPEC in a useful way. Radical surgery, especially in advanced cases, is associated with a high incidence of postoperative morbidity and mortality[34-36], which could even be increased by the HIPEC. HIPEC remains a burdensome procedure: every effort is needed to select patients who will achieve the maximum benefit from it. NAC brings, as a marginal effect, the "*ex-iuvantibus*" determination of chemo-sensitivity of the tumor. This could have a few advantages: for those patients who will certainly not benefit from HIPEC, not to have it. Even if NAC followed by CRS + HIPEC does not show better results in terms of PFS and OS[21,22], valuing the patients' response to NAC could be a strategy to select the patients who showed a chemo-sensitivity to platinum and taxanes for HIPEC only. NAC, by reducing the surgical load, should allow surgery to result in no residual tumor in the vast majority of this set of patients; less required radical surgery is associated with lesser peri-operative complications, permitting a shorter recovery before starting adjuvant chemotherapy; and lastly, this strategy could be offered to a high proportion of women with advanced EOC[2,5].

There are a few studies reporting a total of 334 patients with primary EOC treated with CRS and HIPEC in an up-front setting[1,16,24-30,37-41]. All these phase Ⅱ observational studies included patients where in most cases a great surgical effort has been necessary and the chemo-sensitivity state was unknown: in only 107 cases (36.3%) the patients had undergone NAC to test *in vivo* chemo-sensitivity before CRS + HIPEC.

Bearing in mind the advantages of HIPEC associated with CRS, randomized controlled trials (RCTs) testing its

efficacy have been requested by many clinicians at all time points of the natural history of advanced EOC, especially in up-front settings[6,13,14], as already has been done for colon and gastric cancer[42,43].

Actually, there are five ongoing RCTs evaluating the effectiveness of CRS and/or HIPEC in primary or recurrent EOC[15,44-46]. The one proposed by The Netherlands Cancer Institute (OVHIPEC trial) is intended to evaluate the efficacy of secondary cytoreduction with or without HIPEC[46]. In this study, HIPEC is used in an up-front setting after primary chemotherapy. In our center, a RCT called CHORINE (Cytoreduction and Hipec in the treatment of OvaRIaNcancEr) is starting. This study is a multicenter phase Ⅲ prospective RCT, comparing CRS + HIPEC (cisplatin + paclitaxel) *vs* CRS alone in Stage ⅢC unresectable EOC with partial or complete response after 3 systemic cycles of carboplatin + paclitaxel (NAC), followed by a further 3 cycles of carboplatin + paclitaxel (adjuvant chemotherapy). The primary outcome is two year disease-free survival. Only patients with complete or partial clinical response after the 3 cycles of neoadjuvant therapy are eligible for the study and, after signing the informed consent form, are submitted to CRS with radical intent. The randomization (HIPEC *vs* no HIPEC) will be applied after adequate CRS (residual tumor ⩽ 2.5 mm): patients with suboptimal cytoreduction (residual tumor > 2.5 mm) are not suitable for randomization and will be excluded.

Paclitaxel has been demonstrated to be effective and safe in intraperitoneal hyperthermic use. Different *in vitro* and *in vivo* studies showed that hyperthermia enhances the cytostatic and cytotoxic effect of paclitaxel[47-50]. This drug's characteristics make it a very good candidate to be administered intraperitoneally[51]. Some authors suggest a lower complication rate when paclitaxel is administered in a mono-therapy regimen[52].

On one hand, the advantages of the CHORINE study would be the following: firstly, NAC selects only patients for inclusion in the study in whom there is a clinical response (test of *in vivo* chemosensitivity) and then a response to HIPEC is expected; secondly, the response to NAC should reduce the cytoreductive effort, increasing the occurrence of complete CRS and presumably lowering the morbidity. The reduction of the surgery load after the NAC has been demonstrated to reduce the morbidity but to not influence the OS and the DFS. This probably happens because the macroscopic disease reduced by the NAC is not completely healed. The remnant microscopic disease could be the main cause of disease early progression. The HIPEC treatment has the precise role to reach the diffuse microscopic disease to complete the surgery effort. This is the reason platinum-paclitaxel based chemotherapy is administered. No study has used this combination before; thirdly, the only variable in the study is HIPEC, making it possible to evaluate its effectiveness regardless of CRS, because a radical and complete cytoreduction would be required in either the experimental arm or the control group, as suggested by many authors in the literature[6].

On the other hand, the major limitation of the study is that the control group is not the recognized standard treatment for advanced EOC, namely maximal CRS followed by systemic platinum-based adjuvant chemotherapy. The CHORINE study has already been approved by our review board and we are in the process of completing the administrative requirements and recruiting other participating centers.

CONCLUSION

In conclusion, few studies point out the favorable results in terms of survival after up-front CRS and HIPEC for advanced EOC, but we believe that in the up-front setting, NAC can better select chemoresponsive patients, thus reducing the surgical stress and perioperative complications. Furthermore, by reducing the disease diffusion in responsive patients, NAC could facilitate the dissection and reaching of a real completeness of cytoreduction, evaluated as no macroscopic residual of disease.

REFERENCES

1 **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
2 **Yancik R**. Ovarian cancer. Age contrasts in incidence, histology, disease stage at diagnosis, and mortality. *Cancer* 1993; **71**: 517-523
3 **Cannistra SA**. Cancer of the ovary. *N Engl J Med* 2004; **351**: 2519-2529
4 **Kaplan 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. Philadelphia: Lippincott Williams and Wilkins, 2005: 1364–1397
5 **Abu-Rustum NR**, Chi DS, Curtin JP. Epithelial ovarian cancer. *Curr Probl Surg* 1999; **36**: 1-53
6 **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
7 **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**: 974-999; discussion 974-999
8 **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
9 **Tangjitgamol S**, Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A. Interval debulking surgery for advanced epithelial ovarian cancer. *Cochrane Database Syst Rev* 2010; CD006014
10 **Ansquer Y**, Leblanc E, Clough K, Morice P, Dauplat J, Mathevet P, Lhommé C, Scherer C, Tigaud JD, Benchaib M, Fourme E, Castaigne D, Querleu D, Dargent D. Neoadjuvant chemotherapy for unresectable ovarian carcinoma: a French multicenter study. *Cancer* 2001; **91**: 2329-2334
11 **van der Burg ME**. Advanced ovarian cancer. *Curr Treat Options Oncol* 2001; **2**: 109-118
12 **Polterauer S**, Vergote I, Concin N, Braicu I, Chekerov R, Mahner S, Woelber L, Cadron I, Van Gorp T, Zeillinger R,

Castillo-Tong DC, Sehouli J. Prognostic value of residual tumor size in patients with epithelial ovarian cancer FIGO stages IIA-IV: analysis of the OVCAD data. *Int J Gynecol Cancer* 2012; **22**: 380-385
13 **Elit L**, Oliver TK, Covens A, Kwon J, Fung MF, Hirte HW, Oza AM. Intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a systematic review with metaanalyses. *Cancer* 2007; **109**: 692-702
14 **Armstrong DK**, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, Copeland LJ, Walker JL, Burger RA. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006; **354**: 34-43
15 **Trimble EL**, Alvarez RD. Intraperitoneal chemotherapy and the NCI clinical announcement. *Gynecol Oncol* 2006; **103**: S18-S19
16 **Martin LP**, Schilder RJ. Management of recurrent ovarian carcinoma: current status and future directions. *Semin Oncol* 2009; **36**: 112-125
17 **Leitao MM**, Chi DS. Surgical management of recurrent ovarian cancer. *Semin Oncol* 2009; **36**: 106-111
18 **Bristow RE**, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. *Gynecol Oncol* 2009; **112**: 265-274
19 **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
20 **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
21 **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
22 **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
23 **Kecmanovic DM**, Pavlov MJ, Kovacevic PA, Ceranic MS, Stamenkovic AB. Cytoreductive surgery for ovarian cancer. *Eur J Surg Oncol* 2003; **29**: 315-320
24 **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
25 **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
26 **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
27 **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
28 **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
29 **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
30 **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
31 **Deraco M**, Kusamura S, Virzì S, Puccio F, Macrì A, Famulari C, Solazzo M, Bonomi S, Iusco DR, Baratti D. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as upfront therapy for advanced epithelial ovarian cancer: multi-institutional phase-II trial. *Gynecol Oncol* 2011; **122**: 215-220
32 **Ansaloni L**, De Iaco P, Frigerio L. Re: "cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as upfront therapy for advanced epithelial ovarian cancer: multi-institutional phase II trial." - Proposal of a clinical trial of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in advanced ovarian cancer, the CHORINE study. *Gynecol Oncol* 2012; **125**: 279-281
33 **Markman M**. Platinum-based neoadjuvant chemotherapy for advanced ovarian cancer. *Gynecol Oncol* 2007; **106**: 273-274; author reply 273-274
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
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
36 **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
37 **Steller MA**, Egorin MJ, Trimble EL, Bartlett DL, Zuhowski EG, Alexander HR, Dedrick RL. A pilot phase I trial of continuous hyperthermic peritoneal perfusion with high-dose carboplatin as primary treatment of patients with small-volume residual ovarian cancer. *Cancer Chemother Pharmacol* 1999; **43**: 106-114
38 **Roviello F**, Marrelli D, Neri A, Cerretani D, de Manzoni G, Pedrazzani C, Cioppa T, Nastri G, Giorgi G, Pinto E. Treatment of peritoneal carcinomatosis by cytoreductive surgery and intraperitoneal hyperthermic chemoperfusion (IHCP): postoperative outcome and risk factors for morbidity. *World J Surg* 2006; **30**: 2033-2240; discussion 2033-2240
39 **Lim MC**, Kang S, Choi J, Song YJ, Park S, Seo SS, Park SY. Hyperthermic intraperitoneal chemotherapy after extensive cytoreductive surgery in patients with primary advanced epithelial ovarian cancer: interim analysis of a phase II study. *Ann Surg Oncol* 2009; **16**: 993-1000
40 **Frenel JS**, Leux C, Pouplin L, Ferron G, Berton Rigaud D, Bourbouloux E, Dravet F, Jaffre I, Classe JM. Oxaliplatin-based hyperthermic intraperitoneal chemotherapy in primary or recurrent epithelial ovarian cancer: A pilot study of 31 patients. *J Surg Oncol* 2011; **103**: 10-16
41 **Muñoz-Casares FC**, Rufián S, Arjona-Sánchez Á, Rubio MJ, Díaz R, Casado Á, Naranjo Á, Díaz-Iglesias CJ, Ortega R, Muñoz-Villanueva MC, Muntané J, Aranda E. Neoadjuvant intraperitoneal chemotherapy with paclitaxel for the radical surgical treatment of peritoneal carcinomatosis in ovarian cancer: a prospective pilot study. *Cancer Chemother Pharmacol*

2011; **68**: 267-274
42 **Verwaal VJ**, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2008; **15**: 2426-2432
43 **Yang XJ**, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, Zhou YF, Xiong B, Yonemura Y, Li Y. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. *Ann Surg Oncol* 2011; **18**: 1575-1581
44 Intraoperative hyperthermic intraperitoneal chemotherapy with ovarian cancer trial. ClinicalTrials.gov Identifier: NCT01091636. Available from: URL: http://clinicaltrials.gov/ct2/show/NCT01091636
45 Classe JM, Muller M, Frenel JS, Rigaud DB, Ferron G, Gladieff L. La chimiothérapie intrapéritonéale dans les cancers de l'ovaire. [Intra peritoneal chemotherapy in the treatment of advanced ovarian cancer]. *e-mémoires de l'Académie Nationale de Chirurgie* 2009; 8: 86–90. Available from: URL: http://www.biusante.parisdescartes.fr/acad-chirurgie/ememoires/005_2009_8_1_086x090.pdf
46 Secondary Debulking Surgery +/- Hyperthermic Intraperitoneal Chemotherapy in Stage III Ovarian Cancer. ClinicalTrials.gov identifier: NCT00426257. Available from: URL: http://clinicaltrials.gov/ct2/show/NCT00426257
47 **Bouquet W**, Deleye S, Staelens S, De Smet L, Van Damme N, Debergh I, Ceelen WP, De Vos F, Remon JP, Vervaet C. Antitumour efficacy of two paclitaxel formulations for hyperthermic intraperitoneal chemotherapy (HIPEC) in an in vivo rat model. *Pharm Res* 2011; **28**: 1653-1660
48 **Bouquet W**, Boterberg T, Ceelen W, Pattyn P, Peeters M, Bracke M, Remon JP, Vervaet C. In vitro cytotoxicity of paclitaxel/beta-cyclodextrin complexes for HIPEC. *Int J Pharm* 2009; **367**: 148-154
49 **Cividalli A**, Cruciani G, Livdi E, Pasqualetti P, Tirindelli Danesi D. Hyperthermia enhances the response of paclitaxel and radiation in a mouse adenocarcinoma. *Int J Radiat Oncol Biol Phys* 1999; **44**: 407-412
50 **de Bree E**, Rosing H, Filis D, Romanos J, Melisssourgaki M, Daskalakis M, Pilatou M, Sanidas E, Taflampas P, Kalbakis K, Beijnen JH, Tsiftsis DD. Cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy with paclitaxel: a clinical and pharmacokinetic study. *Ann Surg Oncol* 2008; **15**: 1183-1192
51 **Bae JH**, Lee JM, Ryu KS, Lee YS, Park YG, Hur SY, Ahn WS, Namkoong SE. Treatment of ovarian cancer with paclitaxel- or carboplatin-based intraperitoneal hyperthermic chemotherapy during secondary surgery. *Gynecol Oncol* 2007; **106**: 193-200
52 **Mancebo-González A**, Díaz-Carrasco MS, Cascales-Campos P, de la Rubia A, Gil Martínez J. [Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy associated toxicity in treatment of peritoneal carcinomatosis]. *Farm Hosp* 2012; **36**: 60-67

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