# First-line intraperitoneal cisplatin-paclitaxel and intravenous ifosfamide in Stage IIIc ovarian epithelial cancer

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**Summary**

*Objectives:* To determine the feasibility, toxicity and efficacy of a first-line combination of intraperitoneal (IP) paclitaxel and cisplatin and intravenous (IV) ifosfamide in untreated patients with Stage IIIc ovarian cancer after cytoreduction or biopsies only.

*Methods:* Twenty-six patients entered the trial from 1995 to 1999. Twenty underwent initial cytoreduction which was complete, with residual nodules < 0.5 cm or = 0.5 cm in six, five and nine patients, respectively. Six patients underwent biopsies only at initial surgery. Ten cycles of chemotherapy were planned by both routes. Second-look surgery was planned for all patients.

*Results:* Twenty-one (81%) of the 26 patients were in complete clinical remission (CCR) at the time of second-look surgery. Of the 15 patients who underwent second-look surgery, ten were in CCR including seven in complete remission (CR) confirmed pathologically. Median overall-survival had not been reached at 53 months (range 16-87), and median disease-free survival was 40 months (range 8-85), for a median follow-up of 53 months (range 16-87). Local toxicity consisted mainly of mild abdominal pain. Systemic toxicity was essentially haematological, with eight (31%) grade 3-4 leukopenia.

*Conclusion:* This study has demonstrated the feasibility, moderate toxicity and efficacy of first-line intraperitoneal paclitaxel-cisplatin chemotherapy.

*Key words:* Ovarian cancer; Cisplatin; Paclitaxel; Ifosfamide; Sodium thiosulphate; Intraperitoneal chemotherapy.

## Introduction

The current gold standard for ovarian cancer treatment is a combination of cisplatin (CDDP) or paraplatin and paclitaxel administered intravenously (IV). This combination clearly represents a major step forward in the treatment of this disease [1, 2], but the prognosis remains poor notably in advanced stages with a 5-year survival rate of less than 30 % [3].

The results of trials with high-dose chemotherapy with haematological support have been disappointing [4, 5]. Chemotherapy by the intraperitoneal (IP) route, despite its established pharmacological advantages, with an IP-to-IV plasma concentration ratio from 1 to 3 log for various drugs, is little used [4, 5].

In a randomised study, Alberts *et al.* [6] compared the IV and IP administration of cisplatin (100 mg/m$^2$) with patients receiving cyclophosphamide intravenously. IP-treated patients had eight months longer median survival with a 24% lower risk of death than those treated IV. Other studies have demonstrated the relevance of IP chemotherapy for the treatment of advanced ovarian cancer [6-9]. For most clinicians, these studies [6-9] have failed to change treatment practice. The IP route remains a second-line or consolidation treatment [4-6] restricted to minimal residual tumour masses, although drugs administered intraperitoneally can reach a level of concentration in the blood at least as high as that achieved by IV administration. This is the case for CDDP, which remains the most effective drug against ovarian cancer. The IV adjunction of sodium thiosulphate enables the plasma levels of CDDP administered IP to be raised to levels equivalent or higher than those achieved by IV injection of CDDP [10]. Indeed, tumour destruction by contact is effective only to a depth of a few millimetres, but local cytoxicity is repeated with each IP treatment [10, 11]. Finally, IP chemotherapy becomes an intravenous chemotherapy after having been a contact chemotherapy.

The objective of this study was to evaluate: (a) the feasibility of a combination of paclitaxel and CDDP administered first-line in previously untreated patients with Stage IIIc ovarian cancer (FIGO) by the IP route with a needle, combined with IV ifosfamide (IFO), (b) the complications and toxicity of the IP route, and (c) the preliminary results of this regimen in terms of incidence of relapse and survival.

## Patients and Methods

Twenty-six patients entered this phase II clinical trial from June 1995 to May 1999. The characteristics of the population are summarised in Table 1.

The inclusion criteria were: patients who had never previously received chemotherapy; histologically documented Stage IIIc FIGO (Federation Internationale de Gynécologie et d'obstétrique) carcinoma; obligatory initial laparotomy; age 18 years or older; performance status of 2 or greater (ambulatory and autonomous); adequate renal, cardiac and hepatic functions and a normal blood cell count.

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Table 1. — *Characteristics of the 26 patients with Stage IIIc ovarian cancer, treated with IP paclitaxel-CDDP and IV ifosfamide.*

| | |
|---|---|
| *Age* | 56 |
| (range) | (26-72) |
| *Histology* | |
| Serous | 20 (77%) |
| Endometrioid | 3 |
| Undifferentiated | 2 |
| Mucinous | 1 |
| *Initial Surgery* | |
| Complete | 6 (23%) |
| Incomplete | 20 (77%) |
| Residual masses | |
| < 0.5 cm | 5 (25%) |
| 0.5 - 2 cm | 4 (20%) |
| > 2 cm | 5 (25%) |
| Simples biopsies | 6 (30%) |

*Initial surgery*

All patients underwent a complete resection procedure including peritoneal fluid sampling, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and excision of all visible masses. Second-look surgery was carried out after first-line IP chemotherapy.

If cytoreduction was judged too dangerous due to a large bulk of the tumour and/or widespread peritoneal carcinomatosis requiring intestinal resection, only multiple biopsies were performed. Secondary interval cytoreduction was then planned after first-line chemotherapy.

*Treatment regimen*

Treatment was administered in an outpatient setting over three consecutive days every four weeks. Chemotherapy was administered intraperitoneally in two consecutive litres of liquid (1 litre of normal saline and 1 litre of 5% glucose). CDDP was administered over three days (1/3 of 200mg/m$^2$ given each day) in the first litre of liquid. Paclitaxel (125 mg/m$^2$) was administered on the first day of treatment together with 10 ml of 2% lidocaïne and 120 mg methyl-prednisolone in the second litre. IP chemotherapy was administered either with a lumbar puncture needel or a spring-loaded blunt stylet used to create pneumoperitoneum at laparoscopy. During IP infusion, which takes less than an hour, the patient was given IV over 20 minutes, 125 ml of 5% glucose with 120 mg methyl-prednisolone and 1 ml dexchlorpheniramine to prevent paclitaxel-associated hypersensitivity reactions (1$^{st}$ day only). The patient was also given 50 mg ranitidine and 8 mg ondansetron (each day), followed by one litre 5% glucose supplemented with 30 mg metoclopramide, sodium thiosulphate 5 g/m$^2$/day and ifosfamide 1/3 of 1300 mg/m$^2$ given each day over five hours.

Patients who complained of the slightest abdominal pain during an IP infusion, were given an IV infusion with 2 g of paracetamol. Henceforth, these patients received paracetamol systematically half an hour before the beginning of the IP infusion and were prescribed 1 to 3 g paracetamol to be taken orally, according to the pain for the following days.

Patients were considered to be in complete clinical remission (CCR) when physical examination, CA-125 levels and imaging were normal:

*Second-look laparotomy*

Second-look laparotomy was planned in principle after the tenth cycle of chemotherapy for the patients who underwent initial debulking to evaluate the response to chemotherapy. Complete remission (CR) was defined as the absence of macroscopic lesions and negative histological peritoneal biopsies and peritoneal cytology. All other cases were defined as incomplete remission (IR). The residual masses were classified into two groups according to the tumour size: $< 0.5$ and $\geq 0.5$ cm in diameter.

For patients who underwent only biopsies at exploratory laparotomy, the date of secondary cytoreduction was determined either by tumour reduction as assessed by physical examination, imaging (mainly ultra-sound, CT scan and MRI) and normalisation of monthly CA-125, or to an absence of response to treatment, assessed after at least three cycles of chemotherapy. As for patients who underwent initial debulking, ten cycles of chemotherapy were initially planned.

Regardless of the number of cycles completed before secondary cytoreduction and whatever the results of this secondary surgery, patients agreed to receive the whole treatment initially planned.

*Rescue chemotherapy*

For patients in CR at second-look laparotomy, no further chemotherapy was planned. For patients in IR, rescue chemotherapy delivered by the IP route only was scheduled for three consecutive days every 28 days for six months. The treatment given was a combination of topotecan [12] (1.7mg/m$^2$/day) and oxalyplatin [13] (40mg/m2/day). The same rescue regimen was planned for patients undergoing interval secondary cytoreduction and who would have been in IR after ten cycles of chemotherapy.

*Statistical analysis*

Overall survival and disease-free survival (DFS) were calculated according to the Kaplan-Meier method, and comparisons were made with the log-rank test (and tests of significance with respect to survival distributions were based on the log-rank test). Overall survival was calculated from the date of diagnosis of ovarian carcinoma, established at initial laparotomy, until death. DFS was calculated from initial date of diagnosis until relapse. The end-point of the study was April 2003.

## Results

Tumour response and toxicity data were available for all 26 patients who entered the trial.

*Treatment compliance*

Two hundred and forty-seven cycles of chemotherapy of the 260 scheduled (95%) were administered. The average number of cycles per patient was 9.5 (range 6 to 10). Twenty-one patients received ten cycles. Four patients discontinued treatment for no medical reasons: two patients after six cycles, one after the seventh and one after the eighth cycle.

At first laparotomy 20 patients underwent cytoreduction and six patients had biopsies only.

Of these six patients, before secondary cytoreduction, five patients received 4, 5, 5, 5 and 6 cycles of chemotherapy, respectively. The treatment was then resumed and a total of ten cycles were completed. The sixth patient had received all ten cycles before secondary cytoreduction and was in CR.

*Toxicity*

The dose of chemotherapy was not reduced during the study period. Tables 2 and 3 list the symptoms of local and systemic toxicity observed.

Table 2. — *Frequency of local toxic effects during any course of treatment in the 26 patients.*

| | No. of patients | Grade 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Abdominal pain | 6/26 (23%) | 2 | 4 | | |
| Peritoneal adhesions | 2/15 (13%) | | | | |
| Bacterial peritonitis | 0/26 | | | | |

Table 3. — *Frequency of systemic toxic effects during any course of treatment in the 26 patients.*

| No. of patients | Grade 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Nephrotoxicity | 2/26 (7.7%) | | 1 (3.8%) | |
| Granulocytopenia | 19/26 (73%) | 11 (42%) | 6 (23%) | 2 (7.7%) |
| Thrombocytopenia | 12/26 (46%) | 2 (7.7%) | | |
| Paresthesia | 5/26 (19.2%) | | | |

*Local toxicity*

Abdominal pain occurred in six (23%) patients but was mild in all these cases (grade 1 or 2) and did not require dose modification or narcotic analgesia. It was effectively prevented and/or calmed by IV and oral paracetamol. No bacterial peritonitis or parietal complications were observed. Major adherences were noted in two (13%) of the 15 patients who underwent second-look or secondary cytoreduction.

*Systemic toxicity*

Grade 3 and 4 granulocytopenia was observed in seven (27%) and two patients (7.7%), respectively.

Three patients developed neutropenic fever requiring hospitalisation, G-CSF and antibiotic treatment (infection of the urinary tract in one case, pneumonia in one case and infection of unknown origin in the third case). Thrombocytopenia was mild with only two episodes of grade 2. Due to haematological toxicity, the treatment was delayed by four to seven days (and by 11 days in one patient) in 25 of 247 cycles (10.1%).

Grade 1 nephrotoxicity was observed in two patients and transient grade 3, delaying treatment by ten days, in one patient. Grade 1 paresthesia was seen in six patients (23%).

Vomiting was rare and grade 2 at maximum, as prevention by ondansetron, metoclopramide and methyl prednisolone was highly efficient.

No paclitaxel-related hypersensitivity or paclitaxel-CDDP associated toxicities such as cardiac problems, myalgia, tinnitus or hearing loss were observed.

No treatment-related death occurred in this study.

*Tumour response*

Of the 26 patients, tumour cytoreduction was performed in 20 (77%) patients and biopsies only on the remaining six (23%).

– Surgery was optimal in 11 of 20 patients (55%), macroscopically complete in six patients (30%) and with residual tumour < 0.5 cm in diameter in five (25%) patients. The other nine patients (45%) had residual masses ≥ to 0.5 cm in diameter (0.5 to 2 cm in 4 patients and > 2 cm in 5 patients).

All 26 patients then received first-line chemotherapy, which was adjuvant for the 20 patients who had undergone debulking and neo-adjuvant for the six who underwent simple biopsies.

*Clinical response at second-look or at secondary cytoreduction*

Initially high serum levels of serum CA-125 were found in the 26 patients of the study.

CA-125 serum levels were determined two days before the start of each course of chemotherapy. Initial average CA-125 level was 694 (range: 47 to 11,000). The largest drop in CA-125 level occurred in the first two courses of treatment, whatever the initial level. CA-125 reached normal limits (< 30 U/ml) after two cycles in 12 patients, three cycles in four patients, four in five patients, five in one patient and seven in one patient. In three patients, it remained abnormal. At the time of second-look surgery, 23 patients (88%) had normal serum levels of CA-125 (< 30 U/ml).

Twenty-one of the 26 patients were in CCR after chemotherapy:

– Nineteen of the 20 patients who underwent initial debulking were in CCR at the end of the ten cycles of chemotherapy. The 20$^{th}$ patient had an abnormal CA125 level.

– Two of the six patients who underwent biopsies only were in CCR after four and ten cycles of chemotherapy, respectively. Among the last four patients, the CA 125 level was normal with persistent disease at CT-Scan in two patients and abnormal in two patients.

*Tumour response at second-look or at secondary cytoreduction*

Fifteen (58%) of the 26 patients underwent second-look laparotomy (n = 9) or secondary cytoreduction (n = 6). The response to the chemotherapy is resumed in Table 4.

Table 4. — *Results observed at second surgery (9 second-look and 6 interval secondary cytoreduction) in 15 patients clinically in complete remission after first-line intraperitoneal cisplatin-paclitaxel and intravenous ifosfamide.*

| Initial resection | CCR | SS | Results |
|---|---|---|---|
| *Optimal n = 11* | | | |
| Complete n = 6 | n = 6 | n = 1 | 1 CR |
| < 0.5 cm n = 5 | n = 5 | n = 2 | 2 CR |
| *Suboptimal n = 15* | | | |
| ≥ 0.5 cm n = 9 | n = 8 | n = 5 | 3 CR |
| Biopsies n = 6 | n = 2 | n = 6 | 1 CR |

CCR = complete clinical remission; SS = second surgery; CR = (pathological) complete remission.

Of the 20 patients who underwent initial debulking, 19 patients were in CCR and one had a persistant abnormal CA 125 serum level. Among eight of the 19 patients who underwent second-look laparotomy, six [with initial complete debulking, (n = 1) and residual tumor < 0.5 cm (n = 2) and ≥ 0.5 cm (n = 3)] were in CR and two [with initial residual tumor ≥ 0.5 cm] in IR. For the two patients in IR all persistent lesions were easily removed.

The 20th patient who had an 80 µ/ml CA125 level at the end of chemotherapy had at second-look disseminated residual nodules < 0.5 cm in diameter which could not be removed completely.

All the six patients who underwent only biopsies underwent secondary cytoreduction. One patient was in CR and five in IR. Four of these five patients underwent complete secondary cytoreduction.

*Survival*

Four of the 26 patients died within two years follow-up and six within three years, giving a two and three-year overall survival rate of 85% and 77%, respectively.

Median follow-up for the 26 patients was 55.5 months (range: 16 to 93 months). Of the 26 patients, 19 relapsed (73%) of whom 14 died (one patient died of postoperative haemorrhage), five are alive with progressive disease, and the last seven (27%) patients are disease-free. All the 12 surviving patients have been observed for at least 48 months.

Median disease-free survival (DFS) was 42 months (range: 8 to 91 months) and median overall survival had not been reached at 60 months (range: 16 to 93 months) (Figure 1).

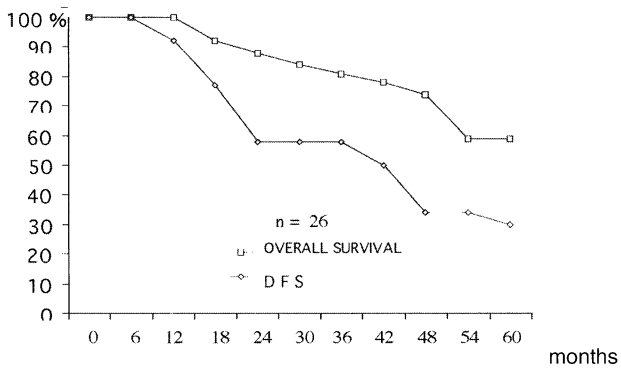


Figure 1. — Disease-free survival and overall survival for the 26 patients treated with IP paclitaxel-CDDP and IV ifosfamide.

For the 11 patients who underwent optimal initial surgery (residual tumor = 0 or < 0.5 cm), median DFS was 49 months (range: 14-91) and median overall survival has not been reached at 60 months (range: 16-91 months).

For the 15 patients who underwent incomplete surgery (9 cases of residual masses ≥ 0.5 cm and 6 patients with biopsies only), median DFS was 37 months (range: 8-66 months) and median survival was reached at 60.2 months (range: 16-93 months).

Due probably to the sample size, up to now no significant difference in median DFS and median survival has been revealed between patients who underwent initial optimal surgery (complete or less than 0.5 cm residual tumour) and patients who had incomplete surgery (residual tumour ≥ 0.5 cm or biopsies).

## Discussion

This study demonstrated the feasibility and safety of IP administration of a first-line paclitaxel and CDDP combination in an outpatient setting. The choice of this protocol was based on the results of other studies [14, 15], showing the efficacy and tolerance of this combination by the IV route (either with platin or paclitaxel administered IP).

Paclitaxel is an attractive drug for IP administration [14-17], because of its pharmacological and clinical characteristics: bulky chemical structure, high molecular weight, a mean IP-to-IV plasma concentration ratio of 1,000, slow elimination from the peritoneal cavity allowing continual exposure of the surface of the tumoural nodules. Recently, a limited systemic exposure to IP paclitaxel was pointed out by Markman *et al.* [18]. However, in vitro studies have demonstrated that paclitaxel concentrations of > 0.05 µmol/l are needed to induce cytotoxic effects [22] and Hofstrat *et al.* [15] with only IP 75 mg/m² obtained peak plasma paclitaxel levels ranging between 0.05 and 0.18 µmol/l. These theoretical effective plasma levels added to the continual exposure of the tumoural nodule surfaces could explain the results obtained with IP paclitaxel [7, 13, 15-20].

With hydration and the protection of sodium thiosulphate [10], there were no problems with CDDP despite the doubling of dose intensity (200 mg/m²) and the tripling of the total dose usually used (2000 mg/m² instead of 600 mg/m²). Markman [7] reported that "despite the renal protection provided by sodium thiosulphate, very little of the *active* CDDP escaping into the systemic circulation is inactivated by the sodium thiosulphate".

Abdominal pain is classically the dose-limiting side-effect of IP paclitaxel at doses of more than 125 mg/m² [20]. In our study local toxicity was moderate because paclitaxel was administered at a dose of no more than 125 mg/m² and abdominal pain was prevented with paracetamol.

As a simple needle was used [8] to administer the IP chemotherapy, we did not observe the complications usually reported with implantable systems such as infection of the implanted material (20%), digestive perforation (1.3-7%), septic peritonitis (4.8-17.6%) and catheter obstruction (2-23.8%) [21, 22]. Extensive peritoneal adhesions, which required adhesiolysis, were present in two (13%) of the 15 patients who underwent second-look surgery or. secondary cytoreduction.

Granulocytopenia was the predominant systemic toxicity. Other systemic toxicities such as neurologic or renal toxicity were efficiently prevented by sodium thiosulphate. With the premedication used, we observed no paclitaxel-related hypersensitivity reactions.

Various factors could be used to evaluate the efficacy of a chemotherapy regimen, including clinical response, changes in CA-125 levels and objective response assessed cytologically and histologically at second-look surgery.

The association of IP paclitaxel-CDDP and IV IFO was effective. In this study, all the 26 patients referred for IP treatment were entered in the trial with no exclusions based on the size of the residual tumour. No case of progressive disease was observed. A good response to this regimen was obtained in all cases, assessed by physical examination and imaging, and in 15 patients by a second surgery. The CCR rate was 81% (21 of 26 patients), which can be compared favourably with rates observed in other series using the IP [5, 6, 9-11, 17] or IV route [1, 2, 5, 9, 14].

It is claimed that patients with small residual nodules benefit the most from IP chemotherapy, but this is also true for IV administration. It also needs to be noted that most reported results concerned patients in the salvage setting [18, 23, 24] when IP chemotherapy is unlikely to be the most effective. In the absence of randomised trials between IP and IV treatment on gross residual tumours no definitive conclusion can be made regarding their impact on tumour reduction and survival. Moreover, in the study of Alberts *et al.* [6] patients who received IP CDDP had a longer survival than those who received IV CDDP whether "tumour masses were 0.5 cm or greater". The authors stated that they did not know the reason but they underlined that their patients were first-line treated. As the difference of median survival between their patients with minimal residual disease (≤ 0.5 cm) treated first-line with IV CDDP (n = 202) or IP CDDP (n = 195) was five months (46 *vs* 51 months), it would have been logical, when adding the patients treated IV (n = 77) or IP (n = 72) with residual tumours of 0.5 to 2 cm, to have had a less beneficial result. Nevertheless, the difference of median survival for all eligible patients was eight months (41 *vs* 49 months). One can suggest that the IP route was at least as effective as the IV route on relatively important residual disease.

Although physical examination and imaging are not very reliable they are of value, particularly with CA-125 monitoring [25], for assessment of the response to treatment. The value of second-look surgery remains doubtful, but this method is still the only way to accurately evaluate the objective response to a treatment [26]. Clearly, there was a poor relationship between the clinical estimation and the pathologic assessment of complete remission at second-look laparotomy, especially when the initial residual lesion was more than 0.5 cm in diameter. Nevertheless, in all cases, a considerable decrease in the size and number of residual lesions was observed at second-look laparotomy. The present study points out the relevance of interval secondary cytoreduction after first-line IP therapy as a mean of enabling optimal surgery, even in patients who only underwent biopsies at initial laparotomy.

No significant difference in DFS and overall survival was noticed between patients who underwent initial optimal surgery (residual lesions = 0 or < 0.5 cm) and patients with residual lesions ≥ 0.5 cm. In the same way, we did not observe a difference in median survival and median DFS between the patients with initial residual lesions = 0.5 cm and those who underwent only biopsies. The lack of significant differences between the "optimal surgery" and "sub-optimal surgery" groups could be explained by the sample size of the present study. In the group of 26 women it is to be underlined that 15 (58%) had lesions ≥ 0.5 cm [0.5 to 2 cm (n = 4); > 2 cm (n = 5) or unresected tumours (n = 6)] at initial laparotomy. The two- and three-year survival rate of 85% and 77%, respectively, can be compared favourably with the report of Rothenberg *et al.* [27]. In their study the two-year survival rate of 85% was obtained on patients with residual lesions ≤ 1 cm maximum treated with IV paclitaxel 135 mg/m$^2$ and by the IP route with paclitaxel 60 mg/m$^2$ and cisplatin 100 mg/m$^2$. In conclusion, our preliminary results suggest that first-line IP chemotherapy with paclitaxel-CDDP and IV IFO is safe and effective in previously untreated patients with Stage III ovarian cancer, even in cases of initial unresectable bulky disease, and can be used in an outpatient setting. These encouraging results have to be confirmed with randomised trials, and the optimal treatment regimen needs to be determined notably in terms of the dose and schedule for paclitaxel.

## References


[1] McGuire W.P., Hoskins W.J., Brady M.F., Kucera P.R, Partridge EE, Look K.Y. *et al.*: "Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with Stage III and Stage IV ovarian cancer". *N. Engl. J. Med.*, 1996, *334* (1), 1.

[2] Neijt J.P., Hansen M., Hansen S.W.: "Randomized phase III study in previously untreated epithelial ovarian cancer FIGO IIb, IIc, III, IV, comparing paclitaxel-cisplatin and paclitaxel-carboplatin". *Proc. ASCO*, 1997, A 1259.

[3] Petterson F., Creasman W.T., Shephard J.H., Pecorelli S.: International Federation of Gynecology and Oncology (eds.). Annual report on the results of treatment in gynecological cancer. Stockholm, Sweden: Editorial Office, Radiumhemmet, 1995.

[4] McGuire W.P.: "How many more nails to seal the coffin of dose intensity?". *Ann. Oncol.*, 1997, *8,* 311.

[5] Ozols R.F., Gore M., Trape C., Grenman S.: "Intraperitoneal treatment and dose intensity in ovarian cancer". *Ann. Oncol.,* 1999, *10* (suppl. 1), 555.

[6] Alberts D.S., Liu P.Y., Hannigan E.V., O'Toole R., Williams S.D., Young J.A. *et al.*: "Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer". *N. Engl. J. Med.*, 1996, *335* (26), 1950.

[7] Markman M.: "Intraperitoneal therapy of ovarian cancer". *Semin. Oncol.*, 1998, *25* (3), 356.

[8] Zylberberg B., Dormont D., Antoine J.M., Madelenat P., Ravina J.H., Uzan S., Salat-Baroux J.: "First line immunochemotherapy with Cisplatin based protocol by intraperitoneal and intravenous routes in ovarian cancer: technique ant results of 82 cases". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 1996, *66*, 57.

[9] Kirmani S., Braly P.S., Saltzstein E.F., Plaxe S.C., Kim S., Kates C., Howell S.B.: "A comparison of intravenous versus intraperitoneal chemotherapy for the initial treatment of ovarian cancer". *Gynecol. Oncol.,* 1994, *54* (3), 338.

[10] Howell S.B., Pfeifle C.L., Wung W.E., Olshen R.A,. Lucas W.E., Yon J.L. Green M.: "Intraperitoneal cisplatin with systemic thiosulfate protection". *Ann. Intern. Med.,* 1982, *97*, 845.

[11] Markman M.: "Intraperitoneal antineoplastic agents for tumors principally confined to the peritoneal cavity". *Cancer Treat. Rev.,* 1986, *13,* 219.
[12] Plaxe S.C., Christen R.D., O'Quigley J., Braly P.S., Freddo J.L., McClay E. *et al.*: "Phase I and pharmacokinetic study of intraperitoneal topotecan". *Invest. New Drugs*, 1998, *16* (2), 147.
[13] Pestieau S.R., Belliveau J.F., Griffin H., Stuart O.A., Sugarbaker P.H.: "Pharmacokinetics of intraperitoneal oxaliplatin: experimental studies". *J. Surg. Oncol.*, 2001, *76* (2), 106.
[14] Hofstra L.S., Bos A.M., de Vries E.G., van der Zee A.G., Beijnen J.H., Rosing H. *et al.*: "Kinetic modeling and efficacy of intraperitoneal paclitaxel combined with intravenous cyclophosphamide and carboplatin as first-line treatment in ovarian cancer". *Gynecol. Oncol.,* 2002, *85* (3), 517.
[15] Kohn E.C., Sarosy G.A., Davis P., Christian M., Link C.E., Ognibene F.P. *et al.*: "A phase I/II study of dose-intense paclitaxel with cisplatin and cyclophosphamide as initial therapy of poor-prognosis advanced-stage epithelial ovarian cancer". *Gynecol. Oncol.,* 1996, *62,* 181.
[16] Francis P., Rowinsky E., Schneider J., Hakes T., Hoskins W., Markman M.: "Phase I feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: a Gynecologic Oncology Group pilot study". *J. Clin. Oncol. Gynecol.*, 1995, *13*, 2961.
[17] Markman M., Rowinsky E., Hakes T., Reichman B., Jones W., Lewis J.L. *et al.*: "Phase I trial of intraperitoneal Taxol: a Gynecologic Oncology Group Study". *J. Clin. Oncol. Gynecol.*, 1992, *10* (9), 1485.
[18] Markman M., Kulp B., Peterson G., Kennedy A., Belison J.: "Second line therapy of ovarian cancer with administered by both the intravenous and intraperitoneal routes: rationale and case reports". *Gynecol. Oncol.*, 2002, *86*, 95.
[19] Rowinsky E.K., Donchower R.C., Jones R.J., Tucker R.W.: "Microtubules changes and cytotoxicity in leukemic cell lines treated with taxol". *Cancer Res.,* 1988, *48,* 4093.
[20] McGuire W.P., Rowinsky E.K., Rosenshein N.B., Grumbine F.C., Ettinger D.S., Armonstrong D.K., Donehower R.C.: "Taxol: A unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms". Ann. Intern. Med., 1989, *111* (4), 273.
[21] Piccart M.J., Speyer J.L., Markman M., Huinink W.T.B., Alberts D., Jenkins J., Muggia F.: "Intraperitoneal chemotherapy: Technical experience at five institutions". *Semin Oncol.*, 1985, *12* (suppl. 9), 90.
[22] Awada A., Guenier C., Nogaret J.M., Kerger J., Tueni E., Sculier J.P. *et al.*: "Cinq années d'expérience avec le port-a-cath intrapéritonéal dans les cancers de l'ovaire : bilan des complications rencontrées". Cancer de l'ovaire - Symposium sur les traitements de seconde intention (Clermont-Ferrand, France), March 23, 1990.
[23] Fennelly D., Aghajanian C., Shapiro F., O'Flaherty C., McKenzie M., O'Connor C. *et al.*: "Phase I and pharmacologic study of Paclitaxel administered weekly in patients with relapsed ovarian cancer". *J. Clin. Oncol.*, 1997, *15,* 187.
[24] Ozols F.. "Cancer epithelial de l'ovaire: données actuelles". Bull. *Cancer,* 1993, *80*, 1.
[25] Rustin G.J.S., Nelstrop A.E., Bentzen S.M., Piccart M.J., Bertelsen K.: "Use of tumours markers in monitoring the course of ovarian cancer". *Ann. Oncol.*, 1999, *10* (suppl. 1), S21.
[26] Nicoletto M.O., Tumolo S., Talamini R., Salvagno L., Franceschi S., Visone E. *et al.*: "Surgical second look in ovarian cancer: a randomized study in patients with laparoscopic complete remission. A Northeastern Oncology Cooperative Group Ovarian Cancer Cooperative Group Study". *J. Clin. Oncol.,* 1997, *15* (3), 994.
[27] Rothenberg M.L., Liu P.Y., Braly P.S., Wilczynski. S.P., Hannigan E.V., Wadler S. *et al.*: "Combined intraperitoneal and intravenous chemotherapy for women with optimaly debulked ovarian cancer: results from an intergroup phase II trial". *J. Clin. Oncol.,* 1997, *21* (70), 1313.

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