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Therapeutic Strategies in Ovarian Cancer

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1. Introduction

Therapeutic management for ovarian cancer (OC) requires effective treatment methods such as optimization in terms of technical variability, dosage, or administration period and the introduction of new therapeutic methods in the existing protocols, all in order to improve immediate results, especially of the long term. Establishing therapeutic strategies are based on the main factors that influence cancer development and prognosis of primary starting point of the ovary. Studies have established even a prognostic profile of OC and a profile of the degree of response to chemotherapy [Spentzos, 2005].

Complex treatment should involve the main therapeutic methods to combat both the primary ovarian tumor and secondary determinations:

- Surgery
- Chemotherapy
- Radiation therapy and recently
- Biological therapy and
- Hormone

The main prognostic factor and therapeutic attitude that divides into two different directions is the set of FIGO stage of disease. With FIGO, a number of other factors require the combination of several methods of therapeutic treatment in the same direction.

2. Therapeutic strategies in early ovarian cancer

OC is confined to early stages I-IIa FIGO. In this stage of OC, therapeutic strategies differ depending on the presence of several prognostic factors, according to which natural evolution of the disease progresses differently. They are represented mainly by:

- FIGO stage
- Grading
- Histology
- Increased amount of ascites
- Preoperative or intraoperative tumor intrusion
- Development of the primary extracapsular tumor
- Patient age

For early stages of OC, Vasey established in 2008 a range of risk depending on the therapeutic attitude that fits (Table 1) [Vasey, 2008].

Good prognosis	Medium prognosis	Poor prognosis
Stage Ia Grade 1 Optimal Staging CA125 ≤ 130	Stage Ib Grade 2 Suboptimal staging	Stage Ic Grade 3 Biopsy only Pre-op rupture Aneuploidy

Table 1. Range in early OC [Vasey-2008].

However, Vergote considered the main prognostic factor tumor grading in tumor recurrence risk, followed in order by preoperative tumor, intraoperative tumor rupture, namely age [Vergote, 2001].

2.1 Radiation

Radiotherapy, either whole abdomen teletherapy or intraperitoneal with ³²P brachytherapy is a method that initially had similar results with combined-modality therapy (CMT), when it was not done with chemotherapy based on platinum ions. Lately it was abandoned due to inferior results and increased risk to platinum-based CMT, in which the rate of major complications locally was increased. Thus, these procedures are currently strict historical interest method [Vergote, 1992; Young, 2003].

2.2 Surgery

OC surgery for early stages follow both the primary tumor, complete excision to the limits cancer and dissemination in the main sites, to their excision or biopsy of their evaluation by sampling [Zoung, 1983; Cass, 2001].

Surgery methods are the following:

- Abdominal hysterectomy with bilateral anexectomy by median approach
- Total omentectomy
- Biopsy pelvic peritoneum (a Pap smear test from the peritoneum fragments from diaphragm is accepted as an alternative method) [Chhieng, 2011].
- Sampling bilateral pelvic and paraaortic lymph nodes
- Lavage cytology of peritoneal cavity
- Appendectomy in all patients with OC epithelial origin, especially if they have mucinous histology or clear cell [Ozols, 2005].

Controversy and debate regarding surgery has occurred for the patients came seeking preservation of reproductive function in these stages. Conservative surgery consisting of unilateral anexectomy is accepted as a therapeutic method in young patients with OC in first stage, with favorable histological structure (low malignant potential, stromal tumors, germinomas) and seeking fertility preservation [Ozols, 2005]. Literature data for carefully and properly selected cases, do not report an increased risk of relapse, or a lower survival rate in patients treated conservatively compared to those treated aggressively [Young, 2003].

If the inspection is suspecting lesion on contralateral ovary in patients treated conservatively, surgical treatment, in addition to unilateral anexectomy should be supplemented by targeted biopsy of suspicious areas [Ozols, 2005]. The presence of tight adhesions between adjacent organs and regional annexes requires the overstaging and the right therapy approach by aggressive surgery and the introduction of adjuvant chemotherapy [Ozols, 2005]. Minimally invasive approach to OC (laparoscopic or robotic) is a therapeutic method that tends to win ever more ground in early stages of OC. Larger studies are needed to analyze the laparoscopic approach compared to the staging and treatment of early OC [Medeiros, 2011]. For patients with favorable prognostic factors (std. Ia, Ib, G1) surgery is considered sufficient as the only therapeutic approach without requiring the association of adjuvant chemotherapy [Young, 2003]. For patients with moderate (std. Ib, G2, suboptimal staging), or with poor prognostic factors (std. Ic, IIa, G3, clear cell carcinoma, close adhesions, break tumor near the operation) surgery is insufficient, requiring adjuvant CMT compulsory association as a therapy method complementary to the management of these cases [Trimbos, 2003].

2.3 Chemotherapy

Chemotherapy as an adjuvant in the treatment protocol of early OC has always been an issue that concerns the role and selection of cases where its use proves its real efficiency in terms of median progression-free survival (PFS) and especially overall survival (OS). The controversies about the application of OC in the early stages CMT year refer specifically to:

- The group of patients to be associated
- Type of CMT and the timing
- Regimens (monotherapy/polytherapy)
- The administration (number of series)

Initially addressed to the patients with the increased prognostic risk groups of early OC, the indication of the application of CMT was extended to patients with moderate risk group due to significant differences in overall survival and median progression-free survival [Young, 2003]. Regarding the timing of CMT in patients with early OC, both technically and as a result, CMT is totally adjuvant; its administration is in fact a therapy nonsense, which would require an initial biopsy laparotomy for a resectable case in radical limits. As an extrapolation of the results obtained with different regimens applied to patients with advanced OC, it was concluded that the most effective combination therapy is the combined protocol Carboplatin AUC 5 to 7.5 mg/ml/min + Paclitaxel 175mg/m²/3h [Kyrgiou, 2006].

Some studies that compared adjuvant CMT versus "watchful waiting", established that the use of adjuvant CMT improves OS and PFS in high-risk patients with early stages of OC. This was confirmed recently by a metaanalysis comprising five prospective randomized studies. Its final conclusion was that the patients who received platinum-based adjuvant chemotherapy had better OS [hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.53-0.93] and PFS (HR 0.67, 95% CI 0.53- 0.84) than patients who did not receive treatment adjuvant [Colombo, 2010]. One of the conclusions of mentioned metaanalysis surprised by considering early adjuvant CMT as a factor influencing the final results in OC, but was very important in the further development of specific cases and suboptimal staging. Later was observed that two thirds of the studies that classified patients of having early stages OC, could classified that patients in higher stages. In these cases there was a significant difference in OS and PFS terms considering association or not adjuvant CMT at initial surgery resection. However, in

suboptimal staged group with unfavorable prognostic factors, adjuvant CMT could address and properly stage the group of patients [Trimbos, 2003]. The controversy regarding the duration of the adjuvant CMT tried to be clarified in GOG-157 study which demonstrated that 6 cycles of Carboplatin + Paclitaxel have the same therapeutic effect (OS and PFS) with only 3 cycles with the same combination, but only with an increased cumulative toxicity [Bell, 2003]. A 33 percent reduction in the risk of loco-regional relapse, demonstrated using the same 6-cycle regimens, compared with 3 cycles, led to the routine use of CMT under standard adjuvant 6 cycles [Bell, 2003].

3. Therapeutic strategies in advanced ovarian cancer

There is a significant difference between the management of early stages and advanced stages of OC management and the latter, there is a difference between stages II B - III C, respectively, stage IV. The inclusion of stage II was made considering prognosis of patients with OC at this stage, and data showed that are closer to those of stage III. For stage II B - III C of OC, therapeutic methods are represented by chemotherapy and surgery, radiotherapy with more historical significance and biological therapy.

3.1 Radiation

Radiotherapy (either WAR or intraperitoneal brachytherapy) was analyzed in several studies, the last completed in 2003. The studies have underlined the utility of this method but also the increased risks of major complications [Verheijen, 2006].

3.2 Surgery

In the early stages of OC, surgery proposed a radical intervention intended to remove the entire tumor, on the one hand, and to estimate the peritoneal dissemination of cancer in any sites for a more accurate staging, on the other hand. In advanced stages, cytoreductive surgery (CRS) has the main purpose not to excise the whole tumor, but to obtain a small volume of residue lesions. Direct proportionality between the individual and the extent of cytoreduction evolution was demonstrated by multiple studies. In 2002, Bristow even proposed a mathematical model, showing that the ultimate goal of surgery is to obtain under 1 cm of residual tumor, which can involve, if feasible, multivisceral resections, peritonectomy, stripping diaphragm, pelvic radical dissection, splenectomy [Marszalek, 2010]. A review on the subject showed an increased OS from 17 to 39 months [Bristow, 2002]. Discussions regarding aggressive surgical risk refer to the degree that is vital for the patient. Thus, if the patient is suitable for CRS at primary laparotomy, then the biopsy is followed by neoadjuvant CMT and subsequently secondary CRS [Tangjitgamol, 2010]. It is preferable that secondary CRS be performed after three cycles of CMT and be followed by three cycles of adjuvant with the same regimen CMT. In patients with complete response to treatment, a second look surgery has not proven be beneficial of the OS. Secondary CRS scheduled after neoadjuvant CMT does not show a clear increased of OS [Winter, 2008].

3.3 Chemotherapy

Chemotherapy is a mandatory means in the treatment of advanced OC. Over time there have been many controversies concerning:

- When administered CMT
- Therapeutic regimes
- Simultaneous therapy versus sequential therapy
- Duration of therapy (no. of cycles)
- Route of administration
- Tumor residue

3.3.1 Timing CMT

The debate is limited not only about using CMT as adjuvant, but also about the possibility of its association as neoadjuvant therapy. Administration of preoperative CMT (preferably 3 cycles) has proven useful only in cases where primary optimal CRS surgery was impossible to perform, and response to treatment favorable, allowing a secondary CRS [Vergote, 2010]. Survival, however, in these cases proved to be a less than optimal in primary CRS cases followed by adjuvant CMT [Kumar, 2010]. The remaining cases that could benefit from primary CRS will receive mandatory six cycles of adjuvant CMT 3 weeks each.

3.3.2 Regimens

Since 1996 it was formulated the standard scheme for CMT in advanced OC, combination of platinum and taxane ions, causing abandonment included Cyclofosamide regimens, doxorubicin or 5-fluorouracil [McGuire, 1996]. The response rates to this combination in patients with advanced OC were different, depending on the degree of primary CRS: 70% for suboptimal CRS and over 80% for primary optimal CRS [Ozols, 2003].

Usefulness of paclitaxel-based chemotherapy potentiation of platinum ions was demonstrated in Gynecologic Oncology Group (GOG) 111 study and European-Canadian (OV-10) trial, but it has not been confirmed by following studies: The Third International Collaborative Ovarian Neoplasm Study (ICON-3) and GOG 132 [McGuire, 1996; Stuart, 1998; Muggia, 2000]. GOG 114 study underlines the effectiveness of carboplatin and cisplatin same regimes combined with a top low toxicity for carboplatin [Ozols, 2003]. In combination with paclitaxel chemotherapy comparing the study above demonstrates increased efficiency of carboplatin in terms of OS and PFS. This is another argument in favor of regime 7.5 Carboplatin/Paclitaxel 175 mg/m²/3h, as concluded in GOG 158 study [Ozols, 2003].

3.3.3 Simultaneous versus sequential therapy

Sequential administration of cytostatics in combination regimens is also an important controversy in the treatment of advanced OC. In GOG-132 study and The European-Canadian study, one of the conclusions was that the benefit of platinum ions taxane association is found both in the system simultaneously, and in the sequence [Vermorken, 2000, Piccart, 2000]. In GOG 132 study was also demonstrated that OS was similar in regimens combined platinum + taxane type ions, regardless of the combination simultaneously, or sequentially, resulting less encouraging for monotherapy (regimes based exclusively platinum ions showing a 5-year OS 67%). The weakest cytostatic agent used as monotherapy was paclitaxel (exclusive regimes showing a 5-year OS 42%) [Vermorken, 2000; Muggia, 2000].

Trial and Randomization	Patient Number	Stage	CCR (%)	Median PFS (months)	Median OS (months)
GOG-111	386	III, IV			
Paclitaxel (135 mg/m ²)			51	18	38
Cisplatin (75 mg/m ²)				P = .0002	P = .0001
Cyclophosphamide (750 mg/m ²)			31	13	24
Cisplatin (75 mg/m ²)	668	IIB IV			
OV10					
Paclitaxel (175 mg/m ²)			50	16	35
Cisplatin (75 mg/m ²)				P = .0005	P = .0016
Cyclophosphamide (750 mg/m ²)			36	12	25
Cisplatin (75 mg/m ²)	2074	Ia IV			
ICON-3					
Paclitaxel (175 mg/m ²)			NA	17.3	36.1
Carboplatin (AUC 5 to 6)				P = .19	P = .74
Carboplatin (AUC 5 to 6)			NA	16.1	35.4a
Cisplatin (50 mg/m ²)					
Doxorubicin (50 mg/m ²)					
Cyclophosphamide (500 mg/m ²)					
GOG-132	614	III IV			
Paclitaxel (135 mg/m ²)			NA	16	35b
Cisplatin (75 mg/m ²)					
Cisplatin (100 mg/m ²)			NA	16.4	30.2
Paclitaxel (200 mg/m ²)			NA	11.4	26

Table 2. Randomized Trials of Paclitaxel versus Non-Paclitaxel First-Line Therapy in Advanced Epithelial Ovarian Cancer [De Vita, 2008].

3.3.4 Duration of therapy (number of cycles)

Three randomized trials that analyzed the effectiveness of increasing the number of cycles of CMT on the OS have concluded unanimously that the results are similar, but increased the frequency of complications (especially neurological). The cumulative toxicity was directly proportional with the number of cycles. It was established that the optimal number of cycles is 6, each separated by 3 weeks of rest between them [Colombo, 2010].

3.3.5 Route of administration

Until recently, the route of administration of the CMT was systemic intravenous peripheral or central. Increasing concentration in the peritoneal cavity of CMT after primary CRS, without causing systemic side effects, is believed to be a result of the ratio of cisplatin, paclitaxel, respectively, between the peritoneum and systemic circulation central. Since then, it appeared the idea of intraperitoneal CMT [Rothenberg, 2003]. Since 1980 analyzed in numerous randomized trials, intraperitoneal administration of CMT was shown to improve OS and PFS in optimal cytoreduced patients and in terms of pathological complete remission in patients in whom cytoreduction was actually, suboptimal (residual tumor < 2 cm was accepted as optimal at that time), compared with only intravenous administration of

CMT [Alberts, 1987]. GOG-172 (Armstrong, 2006) study pointed out that the combination of CMT to the intravenous intraperitoneal resulting OS rise from 49.7 to 65.6 months (35%) and PFS from 19 to 24 months (with 26%), but with a greatly increased associated toxicity. In 58% of cases resulted the abandonment of intraperitoneal administration of CMT, making only 42% complete the 6 cycles (given on day 2 and day 8). Cochrane's metanalysis, balancing risks and benefits, reported in eight randomized trials of systemic administration of CMT (intraperitoneal association and administration) concluded that effect is beneficial in terms of OS (hazard ratio 0.799) and PFS (hazard ratio 0.792) [Jaaback, 2006]. Despite these favorable results, many authors have remained skeptical about this therapy, which was still considered at an experimental level [Gore, 2006; Ozols, 2006]. Since 1994, the efficiency of intraperitoneal CMT is questioned, by administering in hyperthermia. In this respect, there were a lot series of studies that examined the usefulness of this method in the management of OC. CMT administration at 39 to 44,5 degrees Celsius, in addition to increased locoregional and systemic toxic effect, translated into a major complication rate of 28.3% [Ryu, 2004] and a perioperative mortality of 3.7% [Gori, 2005].

HIPEC indications can be summarized in:

- Recurrent or persistent disease: the use of intraperitoneal CMT extended the period of progression of OC lesion from 10 to 21.8 months [Zanon, 2004; Helm, 2007].
- As first-line therapy: although logical, it is recommended an aggressive approach of OC, but when it was applied, the number of cases was too small for a conclusion [Piso, 2004].
- When CRS is scheduled after neoadjuvant CMT, it is preferably an optimal cytoreduction followed by HIPEC. The number of cases remained was insufficient to have a clear conclusion [Reichman, 2005; Yoshida, 2005].
- CMT as consolidation therapy, when it is applicable second look surgery or after a partial response in these cases.

One study observed an improvement from 19.8 to 48.7 months and OS of 52, 8 to 63.4 months (Ryu - cisplatin + interferon treatment) [Ryu, 2004]. These results are relative, since, although in large numbers, the patients from this study were not homogeneous in terms of progress including early cases. Another study obtained a recurrence rate of 69.9% for HIPEC compared with 63.1% in the control group, a difference of OS from 64.4 to 46.4 months, but proved to be insignificant ($p = 0.29$), due to lots of inhomogeneity [Gori, 2005].

Several ways to amend the standard treatment protocols were tried in order that adjuvant CMT to increase:

- Addition of the third chemotherapy
- Management of locoregional chemotherapy
- Maintenance Chemotherapy
- Increasing doses
- The combination of biological therapy

GOG-111 and OV-10 studies identified the need to improve therapeutic strategies considering long-term adverse outcomes [McGuire, 1996; Stuart, 1998].

Combination of the third drug

The combination of the third drug joins the regimen used to treat OC (Carboplatin - Paclitaxel). Other chemotherapy gemcitabine Dacsil, topotecan achieved an improvement

of the OS or PFS, but with a toxicity increased as studies ICON-5 and GOG 182 have shown. The role of the third combination chemotherapy was relevant for mucinous adenocarcinoma OC type or clear cell [Bookman, 2006].

Locoregional administration of CMT

Results of studies on intraperitoneal chemotherapy have been mentioned previously.

Increasing doses of CMT

The concept of increasing doses of CMT has been divided in two: on the one hand, the concept of increasing the dose (increasing the effective dose per chemotherapy cures the same sequentiality) and, on the other hand, the concept of dose densification (the same dose in more frequent cycles). Increasing the desired effect by increasing the dose of chemotherapy was ruled out by the study AGO-Ovar/AIO and EBMT in 2007. The study showed that there were no significant differences in OS and PFS terms [Mobus, 2007]. In 2008, Isonishi and collaborators demonstrated, however, through a study on 631 patients randomized, that in the second year, OS and PFS are significantly influenced (77.7 versus 83.6, respectively 17.1 versus 27.9) after the densification of Carboplatin dosage scheme - Paclitaxel, when these were administered weekly [Isonishi, 2008].

Maintenance therapy

The maintenance therapy requires long term administration, after six cycles of combined CMT or variable number of cycles of CMT administered as monotherapy. Most studies that examined the maintenance therapy with ions of platinum, taxanes, topotecan, epirubicin, surprised no significant differences in OS and PFS terms. One study reported that maintenance therapy for 12 months with Paclitaxel 7 months improved PFS [Markman, 2003; Markman, 2009].

4. Therapeutic strategies in recurrent ovarian cancer

Patients that experienced disease relapse or are refractory to first-line treatment are candidates for second-line chemotherapy. An ideal agent will provide broad antitumor activity, demonstrate a favorable toxicity profile, and have generally convenient administration, among other factors. Additionally, many of the more active agents used in second-line treatment (e.g., gemcitabine, liposomal doxorubicin, and topotecan) are non-cross-resistant to first-line therapies. They exhibit novel mechanisms of action relative to cisplatin/carboplatin and paclitaxel, thereby targeting a different aspect of cell division. The agents include members of the platinum and taxane families, such as carboplatin and paclitaxel (every 3 weeks and weekly schedules), respectively; the topoisomerase I inhibitor topotecan; the liposome-encapsulated anthracycline doxorubicin (liposomal doxorubicin); and the novel antimetabolite gemcitabine. The clinical utility (benefit-risk ratio) of these agents in the recurrent ovarian cancer setting will be reviewed briefly below.

Hexamethylmelamine

Hexamethylmelamine (altretamine; Hexalen; MGI Pharma, Bloomington, MN) is an approved single-agent therapy for ovarian cancer. It has the advantage of oral administration, which may be preferable for some patients. However, it has been

demonstrated only limited activity in patients with relapsed platinum-refractory ovarian cancer [Markman, 2003].

Platinum

Patients that were found to be platinum sensitive at first-line therapy are likely to benefit from reintroduction of platinum on disease recurrence. Both cisplatin (Platinol; Bristol-Myers Squibb, Princeton, NJ) and carboplatin (Paraplatin; Bristol-Myers Squibb) are FDA-approved for the treatment of recurrent ovarian cancer and are often used as monotherapy or in combination with paclitaxel. Carboplatin is considerably less nephrotoxic than cisplatin; however, because the primary route of clearance is renal, the potential for acute renal toxicity should be monitored when it is established the dosage. In clinical trials of single-agent carboplatin, overall tumor response rates ranged from 21% to 30% in platinum-resistant or platinum-refractory patients and from 27% to 53% in platinum-sensitive patients [Williams, 1992; Kavanagh J, 1995; Bolis G, 2001]. Furthermore, the proportion of patients with stable disease was approximately 18% to 33%.

Gemcitabine plus Platinum

Gemcitabine (Gemzar; Eli Lilly and Co., Indianapolis, IN) has received approval in other indications but is still investigational in the treatment of ovarian cancer. Gemcitabine can be safely combined with carboplatin for the treatment of patients with relapsed ovarian cancer [du Bois, 1995]. The gemcitabine plus carboplatin regimen recently compared favorably with carboplatin alone in a randomized trial in patients with relapsed platinum-sensitive ovarian cancer, producing significant improvements in quality of life, significantly faster palliation of abdominal symptoms, significant improvements in response rate, and a significant increase in progression-free survival.

Paclitaxel

- Every three weeks

Paclitaxel (Taxol; Bristol-Myers Squibb) is indicated as first-line (with cisplatin or carboplatin) and subsequent therapy for the treatment of ovarian cancer. The taxane is administered in two different schedules; however, the FDA-approved dosing is intravenous administration over 3 or 24 hours once every 3 weeks. In studies of paclitaxel administered on this schedule, overall tumor response rates were approximately 22% in platinum-resistant or platinum-refractory patients and 45% in platinum-sensitive patients [Cantu 2002; Gore, 1995; Trimble, 1993]. Median survival in platinum-resistant or refractory patients ranged from 6 to 9 months and was 26 months in 47 evaluable platinum-sensitive patients is generally less favorable than it is when the agent is administered weekly; therefore, partly because of the sometimes debilitating toxicity associated with the approved schedule, investigators have developed interest in evaluating the antitumor activity and tolerability of weekly schedules.

- Weekly

Although weekly paclitaxel is not an approved regimen in ovarian cancer therapy, overall tumor responses were at least comparable and potentially higher than those achieved with the every-3-week's schedule in preliminary studies in patients with recurrent disease [Rosenberg, 2002].

Platinum plus paclitaxel

Patients who responded to combination first-line therapy may benefit from reintroduction of platinum and paclitaxel on disease recurrence. In the largest study to date conducted in collaboration with the International Collaborative Ovarian Neoplasm (ICON4) and three cooperative groups, 802 relapsed patients with ovarian cancer were randomized to treatment with platinum plus a taxane or single-agent platinum [Parmar, 2003]. Overall tumor response rate in the combination group was 66% compared with 54% in the platinum treatment group ($P = 0.06$). Notably, the hazard ratios for progression-free survival and overall survival were 0.76 and 0.82, respectively, favoring platinum plus paclitaxel over single-agent platinum in both cases. Thus, there was a statistically significant difference in survival favoring the platinum plus paclitaxel combination compared with single-agent platinum ($P = 0.023$) [Parmar, 2003].

Topotecan

Topotecan (Hycamtin; GlaxoSmithKline, Philadelphia, PA) is an active and well-established agent currently indicated [topotecan (1.5 mg/m^2) on days 1 through 5 of a 21-day cycle] for the treatment of relapsed metastatic ovarian cancer after failure of initial or subsequent chemotherapy.

Docetaxel

Although docetaxel (Taxotere; Aventis Pharmaceuticals Inc., Bridgewater, NJ) is more commonly used in the treatment of non-small-cell lung cancer and breast cancer, recent studies have been conducted in patients with relapsed ovarian cancer [Rose, 2003; Markman, 2003]. In the largest study, with 60 paclitaxel-resistant ovarian cancer patients receiving docetaxel (100 mg/m^2) every 21 days, Rose and collaborators reported a response rate of 22%, including 5% and 17% complete and partial response rates, respectively [Rose, 2003].

Gemcitabine

Although is not currently FDA-approved for the treatment of ovarian cancer, gemcitabine (Gemzar; Eli Lilly and Co.) has typically been administered as monotherapy in pretreated patients with ovarian cancer.

Etoposide

Etoposide (VePesid; Bristol-Myers Squibb) inhibits topoisomerase II and thus inhibits DNA synthesis. In a phase II study in patients with recurrent ovarian cancer investigated etoposide (150 mg/m^2) on days 1 through 3 of a 28-day cycle [Eckhardt, 1990]. Of the 71 patients evaluable for response, 1 achieved a complete response, and 5 achieved a partial response. An additional 48 patients had stable disease.

5. Conclusions

The questions of optimal treatment duration and whether patients should receive treatment to disease progression remain unanswered. However, in the absence of definitive evidence addressing optimal treatment duration in patients with relapsed disease, it should be recognized and appreciated that a number of agents are available that offer a level of

flexibility and treatment customization heretofore unseen in the management of recurrent ovarian cancer in this generally poor-prognosis patient population. These agents should be wielded with the critical goal of balancing the efficacy and toxicity of particular agents and schedules with their effect on symptoms and quality of life.

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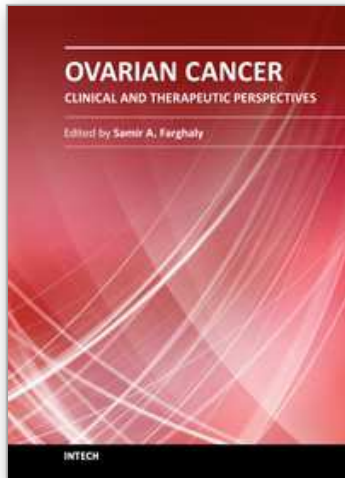
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Ovarian Cancer - Clinical and Therapeutic Perspectives

Edited by Dr. Samir Farghaly

ISBN 978-953-307-810-6

Hard cover, 338 pages

Publisher InTech

Published online 15, February, 2012

Published in print edition February, 2012

Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details the molecular biological aspects of ovarian cancer. It provides molecular biology techniques of understanding this cancer. The techniques are designed to determine tumor genetics, expression, and protein function, and to elucidate the genetic mechanisms by which gene and immunotherapies may be perfected. It provides an analysis of current research into aspects of malignant transformation, growth control, and metastasis. A comprehensive spectrum of topics is covered providing up to date information on scientific discoveries and management considerations.

How to reference

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Dan Ancuşa, Octavian Neagoe, Răzvan Iliina, Adrian Carabineanu, Corina Şerban and Marius Craina (2012). Therapeutic Strategies in Ovarian Cancer, Ovarian Cancer - Clinical and Therapeutic Perspectives, Dr. Samir Farghaly (Ed.), ISBN: 978-953-307-810-6, InTech, Available from: <http://www.intechopen.com/books/ovarian-cancer-clinical-and-therapeutic-perspectives/therapeutic-strategies-in-ovarian-cancer>

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