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Management of Recurrent or Persistent Ovarian Cancer

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1. Introduction

Approximately 70-80% of patients with epithelial ovarian cancer will relapse after first-line chemotherapy with a platinum and taxane-based combination. These patients require further treatment and they may benefit from local and/or systemic therapy. The prognosis is poor and the management of relapsed ovarian cancer remains a difficult problem open to research [National Cancer Institute (NCI), 2010].

Most patients with epithelial ovarian carcinoma receive postoperative chemotherapy, either as adjuvant treatment after complete removal of all visible disease or because of residual tumor. Evaluation after chemotherapy completion includes CA 125 and imaging with chest-X-Ray or CT scanning of the chest and CT scanning or MRI of the abdomen. The limitations of this evaluation are well known. In the past several institutions practiced a "second-look laparotomy", which several times revealed widespread intra-abdominal disease in patients with a negative metastatic work-up. Early detection of persistent disease by second-look laparotomies after completing first-line treatment is no longer practiced, as it had no effect on patients' outcome. The time to first relapse varies from a few months to several years (NCI, 2010). The median interval to first recurrence is 18 to 24 months. Half of the recurrences occur more than 12 months from the end of the first-line therapy, and one quarter of all recurrences occur at less than 6 months. Regarding recurrent sites at first relapse, the primary disease site is involved in fifty-five percent of the patients. Recurrence can also been noted in retroperitoneal or distant nodes, liver, spleen, brain, and bones. In order to clarify prognostic factors and to determine the best treatment approach grouping of recurrent patients has been applied. The results are not clear yet and more publications are needed. (Martin 2009; NCI 2011; Ushijima, 2010).

2. The management of patients with persistent or recurrent disease

Patients with persistent detectable disease after surgery and first-line chemotherapy with a platinum derivative and taxane combination are candidates for further treatment. They have a partial response of residual disease or they have developed progressive disease during first-line chemotherapy. Another group includes patients in complete remission after surgery and first-line chemotherapy who eventually relapse. The management of patients with persistent or recurrent disease is very difficult. In the case of persistent disease the question is what is the proper next step including surgery, chemotherapy and research

protocols. In the case of relapse after a complete response to upfront therapy the first question related to these patients is the best follow-up, the second the time to start treatment and the third the choice of treatment. The goal of treatment today is not the cure but the maintaining or improving the quality of life and prolonging patients' survival. (NCI, 2010; Ushijima, 2010).

As the results of the recurrent disease management remain disappointing the question of maintenance therapy after initial therapy has been raised. After the completion of the initial therapy, surgery and chemotherapy, the majority of patients are in complete remission. This remission in most cases does not last and patients develop recurrent disease. Instead of terminating therapy at this point, the question is if a maintenance, low toxicity therapy, can improve disease free progression and the overall survival. (Gardner & Jewell 2011). Two studies examined the use of paclitaxel in maintenance or consolidation treatment without significant results. There are two ongoing studies with paclitaxel or CT-2103, a polyglutamated taxane and the second with the addition of bevacizumab. Finally vaccines are being studied and they represent a hope to improve today's results (Gardner & Jewell 2011).

2.1 The follow-up of patients completing postoperative chemotherapy

History, physical examination and serial CA 125 determinations at intervals of 1 to 3 months have been accepted as a reasonable follow-up program for patients who are in clinical complete remission. Increases in CA 125 represent a common method to detect disease relapse but as its limitations are well known imaging procedures are also included in many Institutions. (NCI, 2010).

2.2 Detection of disease recurrence and the proper time to start treatment

A well-known analysis of a trial by the Medical Research Council and European Organization for Research and Treatment of Cancer examined the consequences of early institution of treatment for recurrence versus treatment delayed until clinical symptoms appeared. The median survival of all patients registered was 70.8 months. The study concluded that there was no benefit in the detection of early presence of disease by CA 125 (NCI, 2010; Ozols et al., 2003). This is also consistent with the failure of currently tested therapeutic modalities to alter outcome by routine second-look laparotomies and early detection of persistent disease after initial treatment. However it is difficult in everyday practice to follow-up patients with evidence of recurrent disease without treatment and most Oncologists treat their patients without waiting for the symptoms of their disease.

2.3 Therapeutic options

Therapeutic options include local modalities, surgery and radiation therapy, and systemic therapy.

2.3.1 Local modalities: Surgery

Primary cytoreductive surgery and combination chemotherapy are the cornerstones of the initial treatment for epithelial ovarian cancer. Despite advances in the use of chemotherapeutic and biologic agents, surgery remains an important modality in the treatment of recurrent disease as well. (Ramirez et al., 2011). Surgery for clinical recurrence is defined as secondary cytoreductive surgery and it is similar to surgery for persistent

disease at the completion of chemotherapy. The role of secondary cytoreductive surgery for persistent and/or recurrent disease remains unclear. Complete response to chemotherapy for recurrent ovarian cancer is rare, and shrinkage of the tumor does not always prolongs survival while a surgical approach may offer a clear clinical benefit to properly selected patients. So while the results of chemotherapy remain unsatisfactory, especially in platinum resistant patients, several authors have published encouraging results with surgery and the question remains what are the selection criteria for secondary debulking. Are the theoretical and clinical benefits of primary cytoreduction the same in patients with recurrent disease? Do they apply to platinum sensitive and platinum resistant patients as well? What is the definition of limited recurrent disease? How much we can trust the preoperative work-up? What are the results of the cytoreductive surgery in terms of complete resection, optimal resection (residual $\leq$ 1 cm) or suboptimal resection (residual $\geq$1 cm) and what is the relation of these results to the post recurrence survival? Several authors have reported a significant median survival benefit in patients with no or minimal residual disease that ranges from 38 to 61 months compared to 4.5 months to 27 months for suboptimal cytoreduction. In a retrospective study fifty five patients were included who met the following inclusion criteria: A complete clinical response to primary therapy, $\geq$ 12 months between initial diagnosis and recurrence, and $\leq$ 5 recurrence sites on preoperative imaging studies. The conclusions of this study were the definition of localized recurrent ovarian cancer as patients with 1 or 2 radiographic recurrence sites and that in a select population with a diagnosis-to-recurrence interval $\geq$ 18 months and complete secondary cytoreduction the associated median post recurrence survival was approximately 50 months. (Salani et al., 2007).

Due to a lack of large randomized trials, conclusive and universally accepted data are limited regarding the benefits of secondary cytoreductive surgery. A patient with a rapid, multifocal recurrence is unlikely to obtain any clinical benefit from surgery. Secondary cytoreduction should be considered for the subgroup of patients with progressive –free interval of $\geq$12 to 18 months from completion of adjuvant chemotherapy, localized recurrence amenable to complete cytoreduction, potential chemosensitive disease, and good performance status. As with primary debulking, resection to no gross residual disease is the most important prognostic factor. Patients with optimal secondary cytoreduction survived for 16 to 60 months, compared to 8 to 27 months for those patients with residual diseases >1 cm. However the benefit of surgery, compared to chemotherapy alone, is unclear because of a lack of data. The biology of the cancer is certainly another significant cofounding factor (Bae et al., Hoskins et al., 1989; Markman et al, 2004; Frederick et al.; Harter et al; Munkarah & Coleman, 2004).

A subgroup of patients may be candidates for tertiary debulking, based on similar selection criteria used for secondary debulking. (Fotopoulou et al., 2010; Frederick et al 2011). At secondary reduction, bowel or other organ resections are often also performed. More than 30% of surgeries included bowel resection and some of them accompanied considerable morbidity, such as colostomy or pelvic exenteration (Ushijima, 2010).

2.3.2 The management of complications

Small and/or large bowel obstruction is a rather common complication in patients with advanced disease. Surgery in these cases remains controversial and requires careful patient selection. Patients are usually end-stage and malnourished after a period of nausea,

vomiting and constipation. The causes of obstruction are often multifactorial and include mechanical blockage, dense mesenteric infiltration, peritoneal carcinomatosis and adhesions from previous surgery (Ramirez et al., 2011). Surgical procedures include bowel resection, colostomy and intestinal bypass. Even with palliative surgery to remove obstruction, the re-obstruction rate ranges between 10 and 50% (Ramirez et al., 2011). Several patients will definitely benefit from palliative surgery and the absence of the following factors have been associated with successful palliation: 1) More than 3 liters of ascites, 2) Multifocal obstruction, 3) palpable bulky tumors, and 4) preoperative weight loss more than 9 Kg. There are authors who do not agree with these criteria and it remains very important to individualize the approach to a patient with bowel obstruction. Certain patients are candidates for percutaneous gastrostomy only or intravenous hydration and end-stage care (Pothuri et al., 2003; Ramirez et al, 2011).

2.3.3 Local modalities: Radiation therapy

The role of radiation therapy in patients with recurrent ovarian cancer has not been defined. It can be used in selected cases for symptoms palliation.

2.4.1 Systemic therapy

Chemotherapy options for patients with persistent or recurrent disease are subdivided as follows: 1) Platinum-sensitive recurrence: for patients whose disease recurs more than 6 months after cessation of the induction (usually retreated with a platinum (cisplatin or carboplatin) and referred to as potentially platinum sensitive. 2) Platinum-refractory or platinum-resistant recurrence: for patients who progress prior to cessation of induction therapy (platinum refractory) or within 6 months after cessation (platinum resistant); in these patients, platinum derivatives are generally deemed toxic and not sufficiently useful to be part of the treatment plan (NCI, 2010).

2.4.2 Platinum-sensitive recurrence

It has long been recognized that individuals with malignant disease who respond to chemotherapy and who experience a long treatment-free interval before initiation of a second-line treatment program may respond again to the same drug(s) as used in the initial treatment regimen. Ovarian cancer is no exception to this highly clinically relevant observation. (Markman et al, 2004). A number of studies have revealed that secondary responses to platinum-based chemotherapy occur in this setting in as many as 50% to 80% of patients, based on the duration of the treatment-free interval. (Markman et al, 2004). A retrospective study conducted at the Cleveland Clinic has addressed the following question:" Can the duration of the second response in an individual patient be reasonably accurately predicted based on knowledge of the length of the prior response or treatment-free interval?" This study has confirmed the importance of the duration of prior response in defining the opportunity for secondary responses to platinum-based treatment. It has also demonstrated that the duration of response to the initial or prior platinum-based chemotherapy regimen is highly predictive of the upper limit of the duration of response to a subsequent platinum treatment program, assuming that the same or similar drugs are used as in the previous treatment program. The authors note that the large majority of patients in these series received either single-agent carboplatin in the second-line setting or the same drug regimen (carboplatin-paclitaxel) used in the previous course of

chemotherapy. For patients who exhibited an objective response, treatment was frequently discontinued after six courses of therapy. Therefore, it is possible that if platinum had been delivered in combination with an agent not previously administered to that individual or if the drug had been continued in the responding patient population, the duration of response might have been longer. (Markman et al, 2004). They suggest that more data are required. However, they note, although prolonging second-line therapy or adding a new drug may improve the duration of response, either approach also has the potential to increase both the toxicity and the cost of treatment without having any meaningful impact on the patient's quality of life, time to symptomatic disease progression, or overall survival. (Markman et al, 2004). These series have been unable to accurately predict the duration of secondary response to platinum chemotherapy for individual patients based on the length of the initial or immediately preceding remission. Although this may have been because of the limited number of patients in each previous response duration category, it is also possible that inherent substantial heterogeneity associated with the recurrent tumor (e.g. the rate of growth of platinum-resistant cells present within the sensitive tumor cell population) makes it unrealistic that a reliable predictive model for individual patient management can be developed. (Markman et al, 2004). This study has several potential implications for clinical trials design for second-line chemotherapy.

Several studies that have been conducted in patients with recurrent platinum sensitive ovarian carcinoma, have reinforced using carboplatin as the treatment core for patients with platinum-sensitive recurrences (Muggia, 1989). Cisplatin is occasionally used, particularly in combination with other drugs, because of its lesser myelosuppression, but this advantage over carboplatin is counterbalanced by its greater intolerance. Oxaliplatin, initially introduced with the hope that it would overcome platinum resistance, has activity mostly in platinum-sensitive patients (Piccart et al., 2000) but has not been compared with carboplatin alone or in combinations. With all platinums, outcome is in generally better the longer the initial interval without recurrence from the initial platinum-containing regimens (Markman M et al., 2004).

However the clinical benefit based on the progression free survival (PFS) and the overall survival (OS) is in generally limited.

The combination of Carboplatin and pegylated-liposomal doxorubicin have resulted in a median PFS of 9 months and a median OS of 31 months (Ferrero et al, 2007). The combination of Carboplatin and Epirubicin versus Carboplatin produced a very limited difference in OS 17 versus 15 months (Bolis et al, 2001). A triple combination of Cisplatin, doxorubicin and cyclophosphamide (CAP) that has been used in the past as first-line treatment of choice versus paclitaxel revealed a significant difference in both PFS 15.7 versus 9 months and in OS 34.7 versus 25.8 months (Cantù et al., 2002). The addition of Gemcitabine to Carboplatin was compared to Carboplatin alone. The PFS was 8,6 versus 5.8 month and the OS 18 versus 17 months (Pfisterer et al, 2006).

In an international, multicenter trial 802 patients were randomized to receive paclitaxel plus platinum chemotherapy or conventional platinum-based chemotherapy. The paclitaxel plus platinum combination seems superior in terms of PFS and median OS. The PFS was 11 versus 9 months and the OS 24 versus 19 months in the two groups (Parmar et al, 2003). Accordingly, because of this randomized experience, carboplatin plus paclitaxel is considered the standard regimen for platinum-sensitive recurrence in the absence of residual neurotoxicity.

Platinum derivatives remain the most important drugs in the management of recurrent ovarian carcinoma. It is of interest that on occasion, patients with platinum-sensitive recurrences relapsing within 1 year have been included in trials of nonplatinum drugs. In one such trial, comparing the pegylated liposomal doxorubicin (PLD) to topotecan, the subset of patients who were platinum sensitive had better outcomes with either drug (and in particular with PLD) relative to the platinum-resistant cohort (Gordon et al., 2004).

2.4.3 Platinum-refractory or platinum-resistant recurrence

Clinical recurrences that take place during or within 6 months of completion of a platinum-containing regimen are considered platinum-refractory or platinum-resistant recurrences respectively. Patients with originally platinum- sensitive disease eventually also become platinum-resistant. Anthracyclines (particularly when formulated as PLD), taxanes, topotecan, and gemcitabine are used as single agents for these recurrences. These agents in generally convey a marginal benefit. Patients with platinum-resistant disease should be encouraged to enter clinical trials. Treatment with paclitaxel historically provided the first agent with consistent activity in patients with platinum-refractory or platinum-resistant recurrences (Kohn et al., 1994; McGuire et al., 1989, Einzig et al., 1992, Thigpen JT et al., 1994, Trimble EL et al., 1993).

Subsequently, randomized studies have indicated that the use of topotecan achieved results that were comparable to those achieved with paclitaxel. In phase II studies, topotecan administered intravenously 1.5mg/m^2 on days 1 to 5 of a 21-day cycle yielded objective response rates ranging from 13% to 16.3% and other outcomes that were equivalent or superior to paclitaxel (Ten Bokkel Huinink W et al, 1997, Kudelka AP et al.; 1996, Creemers et al.; 1996, Bookman et al., 1998). Substantial myelosuppression follows administration in most cases. Other toxic effects include nausea, vomiting, alopecia, and asthenia. A number of schedules are under evaluation in an effort to decrease hematologic toxicity (NCI, 2010). Topotecan was compared with pegylated liposomal doxorubicin in a randomized trial of 474 patients and demonstrated similar response rates, PFS, and OS at the time of the initial report, contributed primarily by the platinum-resistant subsets (Gordon et al., 2001).

A phase II study of Pegylated liposomal doxorubicin (PLD) given IV 50mg/m^2 once every 21 to 28 days demonstrated one complete response and eight partial responses in 35 patients with platinum-refractory or paclitaxel-refractory disease (response rate = 25.7%). In general, liposomal doxorubicin has few acute side effects other than hypersensitivity. The most frequent toxic effects are usually observed after the first cycle and are more pronounced following dose rates exceeding 10 mg/m^2 per week and include stomatitis and hand-foot syndrome. Neutropenia and nausea are minimal, and alopecia rarely occurs. (Muggia et al., 1997). Liposomal doxorubicin and topotecan have been compared in a randomized trial of 474 patients with recurrent ovarian cancer. Response rates (19.7% versus 17.0%; P = .390), PFS (16.1 weeks vs. 17.0 weeks; P = .095), and OS (60 weeks versus. 56.7 weeks; P = .341) did not differ significantly between the liposomal doxorubicin and topotecan arms, respectively. Survival was longer for the patients with platinum-sensitive disease who received liposomal doxorubicin (Gordon et al., 2001,2004).

Docetaxel has shown activity in paclitaxel-pretreated patients and is a reasonable alternative to weekly paclitaxel in the recurrent setting (Berkenblit et al., 2004).

Several phase II trials of gemcitabine as a single agent administered IV on days 1, 8, and 15 of a 28-day cycle have been reported. The response rate ranges from 13% to 19% in

evaluable patients. Responses have been observed in patients whose disease are platinum refractory and/or paclitaxel refractory as well as in patients with bulky disease. Leukopenia, anemia, and thrombocytopenia are the most common toxic effects. Many patients report transient flu-like symptoms and a rash following drug administration. Other toxic effects, including nausea, are usually mild (Friedlander et al., 1998; Lund et al., 1994; Mutch et al., 2007, Shapiro et al., 1996).

Ovarian cancer patients generally receive paclitaxel in front-line induction regimens. Retreatment with paclitaxel, particularly in weekly schedules, indicates an activity comparable to those of the preceding drugs. If there is residual neuropathy upon recurrence, this may shift the choice of treatment towards other agents. In a phase III study, 235 patients who did not respond to initial treatment with a platinum-based regimen but who had not previously received paclitaxel or topotecan, were randomly assigned to receive either topotecan as a 30-minute infusion daily for 5 days every 21 days or paclitaxel as a 3-hour infusion every 21 days. The overall objective response rate was 20.5% for those patients who were randomly assigned to treatment with topotecan and 13.2% for those patients who were randomly assigned to treatment with paclitaxel (P = .138). Both groups experienced myelosuppression and gastrointestinal toxic effects. Nausea and vomiting, fatigue, and infection were observed more commonly following treatment with topotecan, whereas alopecia, arthralgia, myalgia, and neuropathy were observed more commonly following paclitaxel (Ten Bokkel Huinink et al., 1997).

2.4.4 Other drugs used to treat platinum-refractory or platinum-resistant recurrence

This group includes drugs that have limited activity in platinum-resistant cases but they are in use in every day practice as there are patients who need successive chemotherapeutic regimens. 1) Etoposide. It can be given intravenously or orally. It has limited activity. 2) Cyclophosphamide. It was used as first-line therapy in combination with platinum derivatives in the before the paclitaxel era. It has uncertain activity in platinum resistant cases. 3) Hexamethylmelamine (Alteramine) is an alkylating prodrug, has also uncertain activity in platinum resistant cases. 4) Irinotecan. It is cross - resistant to topotecan. 5) Oxaliplatin. Partially cross -resistant to the other platinum derivatives. 6) Vinorelbine. 25-30mg/m^2 IV on days 1 and 8 every 21 days. Vinorelbine can also be given orally. It has erratic activity. 7) 5-fluorouracil and capecitabine. May be useful in mucinous tumors. (Vasey et al., 2003). 8) Tamoxifen. Has minimal activity. May be useful in certain cases either after chemotherapy or in older patients who do not tolerate or refuse to receive chemotherapy 9) Trabectedin (*Yondelis*) a new drug for advanced soft-tissue sarcomas in combination with liposomal doxorubicin has shown significant activity in patients with relapsed ovarian carcinoma and has been approved for use in certain countries. It was however rejected by a US Food and Drug Administration (FDA) advisory committee. Further clinical trials are needed. 10) Thalidomide an antiangiogenic agent in combination with Topotecan appears to improve response rate in patients with recurrent ovarian cancer. The results of phase III are needed (Downs Jr LS 2007).

2.4.5 Hyperthermic intraperitoneal chemotherapy

Patients with widespread peritoneal carcinomatosis present a very difficult problem as cytoreductive surgery has limited results. A retrospective study suggests that the combination of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is

feasible and has potential benefits. A randomized trial is needed to establish its role in the management of these difficult cases (Chua, et al 2009). Similar results were reported in a pilot study of Oxaliplatin-based hyperthermic intraperitoneal chemotherapy in recurrent epithelial ovarian cancer. It proved to be feasible, relatively safe and effective in combination with chemotherapy and surgery in cases with peritoneal carcinomatosis (Frenel, et al 2011). Larger studies are needed (Roviello, et al 2010).

2.4.6 New drugs – Targeted therapy

Certain studies evaluating the efficacy of antiangiogenic agents in ovarian cancer have been reported including vascular endothelial growth factor (VEGF) pathway inhibitors, monoclonal antibodies, tyrosine kinase inhibitors and inhibitors of other angiogenic factors and vascular disrupting agents. Angiogenesis is a critical component of tumor development and proliferation. Agents that target the angiogenic process are of considerable interest in the treatment of ovarian cancer. Bevacizumab is a humanized monoclonal antibody against VEGF and possesses minimal single-agent activity in common epithelial cancers such as colorectal, non-small-cell lung cancer and breast cancer. The combination of Bevacizumab with chemotherapy has revealed significant improvement in the outcome in several tumors, leading to registration. Bevacizumab possesses more single-agent activity in epithelial ovarian cancer than in any other epithelial tumor, apart from renal cancer, where the vascular biology is specifically relevant to this therapeutic approach. Clinical trials have confirmed Bevacizumab effectiveness but that also revealed significant toxicity including bowel perforation. (Kaye ., 2007; Teoh et al., 2011; Monk et al., 2006).

Three phase II studies have shown activity for Bevacizumab, an antibody to vascular endothelial growth factor (VEGF). The first study included 62 patients who had received only one or two prior treatments (these last patients had received one additional platinum-based regimen because of an initial interval of 12 months or greater after first-line regimens and also had to have a performance status of 0 or 1)(Burger et al., 2007). Patients received a dose of 15 mg/kg every 21 days; there were two complete responses and 11 partial responses, a median PFS of 4.7 months, and an OS of 17 months. This activity was noted in both platinum-sensitive and platinum-resistant subsets. The second study only included patients with platinum-resistant disease using an identical dose schedule, but the study was stopped because five of 44 patients experienced bowel perforations, one of them fatal; seven partial responses had been observed (Cannistra et al., 2007). This increased risk of bowel perforations was associated with three or more prior treatments (Monk et al., 2006; Kaye 2007). The third study included 70 patients who received 50 mg of oral cyclophosphamide daily, in addition to bevacizumab (10 mg/kg every 2 weeks); 17 partial responses were observed and four patients had intestinal perforations. (Garcia et al., 2008). Studies by the Gynecologic Oncology Group are evaluating the efficacy of the drug added to the initial treatment and at first recurrence in the platinum-resistant setting. Bevacizumab will probably be approved for clinical use in the near future. As neovascularization is a complicated process other antiangiogenic agents have been developed to overcome resistance to VEGF blockade, and several are undergoing clinical trials (Teoh et al., 2011). Future studies must answer to the following questions: The role of bevacizumab in first-line treatment and in the management of recurrent disease, the results of the combination with chemotherapy, risk factors for bowel perforation, the appropriate dose 15mg/Kg every three weeks or less and criteria for patient selection for bevacizumab treatment. (Kaye., 2007; Teoh et al., 2011; Monk et al., 2006).

Several targeted therapeutic agents are under evaluation in ongoing studies. They include the following groups of agents: 1) Antiangiogenic agents, 2) mTOR inhibitors, 3) PARP inhibitors and 4) Histone Deacetylase inhibitors.

1. Antiangiogenic agents include: a) Bevacizumab which has already been presented and will probably be approved for clinical use in the near future. b) VEGF-Trap a potent angiogenesis inhibitor fusion protein is under study. c) Agents that block the VEGF receptor. These agents include sorafenib and sunitinib, small molecules that block tyrosine kinase activity located in the cytoplasmic domain of VEGF receptor (VEGFR). Some of these molecules block VEGFR specifically, whereas others, such as sorafenib and sunitinib, block both VEGFR and the platelet-derived growth factor (PDGFR), thought to be involved in later phases of tumor angiogenesis relating to vessel maturation. (Gardner & Jewell, 2011).
2. mTOR inhibitors. Dysregulation of mTOR signaling occurs in many tumors and has been found to be activated in gynecological cancers. Increased AKT/PI3K activity with constitutive downstream activation of the mTOR pathway has been found in ovarian tumor specimens and ovarian cancer cell lines. Inhibition of mTOR by agents such temsirolimus, everolimus and deforolimus are in clinical trials.(Gardner & Jewell, 2011).
3. PARP inhibitors. Inhibition of poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP), a key enzyme in the DNA repair, may lead to the accumulation of breaks in double-stranded and cell death. Therefore, PARP inhibitors have been developed and are potentially exciting agents in the treatment of ovarian cancer, especially cancers with BRCA1 and BRCA2 mutations. Initial reports have been encouraging A phae II, randomized double-blind, multicenter study is assessing the efficacy of an oral PARP inhibitor olaparib (AZD2281) in the treatment of patients with platinum-sensitive serous ovarian cancer following treatment with two or more platinum-containing regimens. (Gardner & Jewell, 2011).
4. Histone Deacetylase Inhibitors. Aberrant histone modifications such as hypoacetylation have been associated with malignancy through the transcriptional silencing of tumor suppressor genes. Belinostat is a histone deacetylase inhibitor (HDAC) that can alter the acetylation level of histone and nonhistone proteins. Such epigenetic modulation may sensitize drug-resistant tumor cells to other antineoplastic agents, as suggested in preclinical studies. A phase II study is examining the use of belinostat in combination with carboplatin among patients with recurrent or persistent platinim-resistant disease. (Gardner & Jewell, 2011). These new targeted biologic agents, particularly those involved with the vascular endothelial growth factor pathway and those targeting the poly (ADP-ribose) polymerase (PARP) enzyme, hold great promise for improving the outcome of ovarian cancer. (Jelovac & Armstrong 2011).

2.4.7 Microarray – Based gene expression studies in ovarian cancer

Despite recent improvements in treatment, ovarian cancer remains the No. 1 cause of death among gynecologic cancer in the United States. In more than 90% of patients with localized disease, surgery alone is curative. However, in most patients, the tumor has disseminated beyond the ovaries by the time the cancer is diagnosed. For these patients combined modality treatment, surgery and chemotherapy, is necessary and first-line chemotherapy has yielded response rates of greater than 80%. Unfortunately the median progression-free survival has been only 18 months in these patients and, in most with advanced cancer, the

disease eventually relapses and the patient dies. Studies evaluating various cytotoxic agents in recurrent ovarian cancer have generally shown responses of 10% to 28% with limited effect on overall survival. This has prompted the search for novel strategies for treatment of ovarian cancer. (Chon & Lancaster, 2011).

Since 1987 microarray technology has been deeply incorporated in research settings and is developing an increasing presence in clinical arenas. Prior to the era of microarrays, the approach to understanding carcinogenesis largely focused on studying one gene at a time. Measuring the expression of thousands of genes at the same time using microarrays has answered many questions that were impossible to resolve previously. Gene expression assays are now used in daily clinical practice in the care of many patients who are newly diagnosed with breast cancer. In ovarian cancer, gene expression profiles have so far been used to examine differential gene expression patterns between histology subtypes. Several studies have sought to identify gene expression signatures that correlate with clinical outcome, to determine which genes affect survival and relapse, and to generate biomarkers that could predict patient response to chemotherapy. Data from these studies have deepened and widened our understanding of the biology of ovarian cancer despite some challenges. Studies on the role of microarray analysis to identify gene expression profiles associated with prognostic values and prognostic and predictive molecular markers will help identify patient groups who could benefit more from individualized treatment rather than the current standard first-line chemotherapy. In addition, identification of biomarkers associated with early detection of disease and molecular subsets will also improve overall survival for patients with ovarian cancer, as the early signs of the disease are often undetectable. (Chon & Lancaster, 2011).

2.4.8 Ovarian cancer: The future

Over the last several decades, clinical trials have led in 2006, for the first time, to a median overall survival of greater than 5 years in advanced – stage patients treated in a randomized controlled trial (Gardner & Jewell, 2011). Clinical trials continue to address important questions including the following issues: 1) The combination of surgery and chemotherapy. 2) The identification of new targeted therapeutics. 3) The route and timing of chemotherapy administration. 4) The quality of life endpoint 5) Tissue acquisition for translational studies. (Gardner & Jewell, 2011).

Quality of life studies. Persistent or recurrent ovarian cancer is not a curable disease today. The first aim of the Oncologist must be the improvement or maintenance of the quality of patients' life and the second the survival increase. There are at least 78 ongoing studies on quality of life today. The burden of disease and the effects of treatment have been increasingly recognized. Clinical trials are increasingly including quality of life components in trial designs in an effort to increase the duration of life and improve its quality at the same time. (Gardner & Jewell, 2011). Health – related quality of life (HRQOL) addresses important aspects of the patient's life including physical, social, psychological, financial, and sexual issues, as well as the side effects of the chemotherapeutic medications that we rely on for treatment. (Grzankowski & Carney, 2011). HRQOL assessment plays an important role in medical care, and this is especially significant in ovarian cancer treatment as 80% of newly diagnosed patients present with advanced disease and require extensive surgical and chemotherapeutic treatment regimens that are associated with significant morbidity. (Grzankowski & Carney, 2011). HRQOL data can be utilized in clinical trials, with an

endpoint of improvement of HRQOL. The data can also be used as a tool in standardizing the efficacy and tolerability of treatment. In addition, information from the HRQOL assessments may help identify the need for changes in treatment regimens that may have otherwise been overlooked and can aid in the deciding when to pursue need for further treatment versus palliative care. (Grzankowski & Carney, 2011). Prolongation of life, without regard for the quality of that life, is not a universally desired goal. When considering aggressive, life-prolonging treatments and end-of-life decisions, it is necessary to consider each individual's assessment of what makes life worth living. Overall HRQOL assessment can help patients with ovarian cancer maintain autonomy when faced with the difficult decision between aggressive, life – prolonging treatments versus end-of-life decisions. As medical, pharmaceutical, and surgical techniques continue to prolong life much longer than our predecessors would have imagined, it is now the role of today's physicians to encompass quality of life into their ever-changing role as health care providers and patient advocates. To reach such positive outcomes, the use of an interdisciplinary treatment team approach is vital to each patient's needs. To optimize treatment decisions for patients with ovarian cancer, clinicians need to be familiar with differences between regimens in terms of toxicity, dosage, and administration, and emerging data from HRQOL assessments. (Grzankowski & Carney, 2011).

While decisions surrounding the diagnosis and treatment of cancer are difficult and cost is not usually the most pressing concern of decision makers, the increasing burden of the rising cost of healthcare demands attention. As newer, higher-cost therapies become available, formal evaluation of the costs and benefits of these new treatments in comparison to existing and established strategies should be a high priority. (Sfakianos et al, 2011).

2.5.1 Treatment options for patients with persistent or recurrent disease

There are today three available treatment options, as presented above, for patients with persistent or recurrent disease than can be used alone or in combination:

a. Secondary cytoreduction.
b. Chemotherapy. For patients with platinum-sensitive disease treatment with a cisplatinum or carboplatin combination is indicated. For patients with platinum-refractory or platinum-resistant disease treatment with other effective drugs must be used.
c. Clinical trials.

3. Conclusions

Patients with persistent or recurrent ovarian cancer have a lethal chronic disease. Treating them is challenging, and despite the recent advances many controversies remain. Research findings continue to resolve many of these issues. Secondary cytoreduction, especially complete, combined with further adjuvant therapy at the time of relapse may improve clinical outcome in selected patients. There are several treatment choices from first relapse to terminal state; however these choices cannot be made uniformly. They should be decided on an individual basis depending directly on the patients' condition. Patients with recurrent platinum-sensitive ovarian cancer have significant response rates and longer PFS when treated with combination platinum-based chemotherapy. Most recurrent patients with platinum resistant disease have little chance for a long PFS, but treatment may contribute to extending their overall survival.

Finding the optimal treatment remains a research goal.

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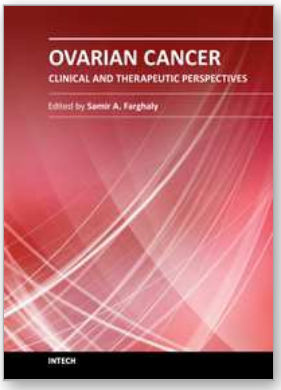

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Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details 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.

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