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Progress in ovarian cancer: an overview and perspective

R.F. Ozols*

Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111, USA

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Abstract

Ovarian cancer remains the number one gynecologic killer in the Western world. However, there has been significant progress in understanding the genetics of ovarian cancer and in development of more effective therapies. The current optimum approach to therapy consists of cytoreductive surgery followed by combination chemotherapy. Clinical trials have established that carboplatin plus a taxane (usually paclitaxel) can be considered to be the treatment of choice for most patients with advanced disease. Most patients will achieve a clinical complete remission with such a combination. However, the median time to progression is less than 2 years, and for patients with optimal stage III disease, median survival will be approximately 5 years. Clinical trials are currently evaluating new combination chemotherapy regimens and the role of maintenance therapy in improving time to progression and overall survival. There has been a great deal of progress in understanding the genetics of epithelial ovarian cancer. The relationship between mutations in *BRCA1* and *BRCA2* genes and inherited predisposition to ovarian cancer has been of major clinical importance. While 90% of ovarian cancer cases are still considered to be sporadic, identification of the molecular events associated with hereditary ovarian cancer will lead to an increased understanding of the pathogenesis of sporadic disease as well since the two diseases share many clinical features. Development of high throughput screening methodology, such as CDNA microarray analysis, will lead to identification of additional genes which are important in the development of ovarian cancer, and will help define new targets for therapy and prevention as well as potential new biomarkers for early detection. The next generation of clinical trials will be focused on evaluating chemotherapy together with new molecular therapies, such as signal transduction inhibitors, anti-angiogenesis agents, and inhibitors of matrix metalloproteinases.

Keywords: Ovarian oncogenesis; Chemotherapy; Molecular targeting

1. Introduction

Ovarian cancer is the number one gynecologic killer in the Western world. In the United States, it is estimated that there will be 24 000 new cases in 2002 with approximately 14 500 deaths [1]. Despite improvements in the management of patients with ovarian cancer, the mortality rate is essentially unchanged over the last two decades. The primary reason for the high mortality rate from ovarian cancer is the fact that most patients (approximately 75%) present with metastatic disease (FIGO stages III and IV) at the time of diagnosis. The common epithelial ovarian cancers arise from the surface epithelial cells of the ovary and malignant cells escape from the surface capsule and disseminate throughout the peritoneal cavity without producing signs or symptoms. Dissemination of disease also occurs via pelvic and para-aortic lymph channels and, less frequently, haematogenously. This pattern of metastasis contributes to the difficulties in early detection, and most patients present with signs and symptoms of late-stage disease, including bowel dysfunction and abdominal distention. Early detection is being evaluated in clinical trials with serum CA-125 levels and transvaginal sonograms; however, at this point, there is no evidence that screening the general population is effective in reducing morbidity and/or mortality from this disease [2]. Consequently, routine screening is not recommended.

Surgery continues to have a major role in the management of patients with ovarian cancer, both for accurate staging and for removal of bulk disease (cytoreduction). However, most patients with advanced-stage disease invariably have residual disease, either macroscopic or microscopic, despite maximal attempts at cytoreduction. Most patients are treated with

* Tel.: +1-215-728-2673; fax: +1-215-728-5346.
E-mail address: r_ozols@fccc.edu (R.F. Ozols).

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chemotherapy following surgery as ovarian cancer has been shown to be a highly drug-sensitive disease. In contrast to many other metastatic epithelial diseases where the combination of surgery and chemotherapy leads to a few patients achieving a clinical complete remission, the majority of patients with ovarian cancer are in a clinical complete remission following surgery and induction chemotherapy. However, relapses from a complete remission are frequent, and it is estimated that only 20–25% of patients with advanced-stage disease will be alive in 10 years. While the combination of cytoreductive surgery and chemotherapy has not significantly improved long-term survival for patients with advanced disease, it is of note that a significantly larger percentage of patients survive 5 years with current management approaches than was the case two decades ago. It has been estimated that in the 1960s approximately one-third of patients survived 5 years, and with current treatment more than half the patients will be alive at the 5-year mark. Consequently, ovarian cancer is frequently considered to be a chronic disease, and while cure remains the ultimate goal of cancer therapy, prolongation of survival, together with palliation of symptoms, is a clinically meaningful accomplishment.

2. A etiology of ovarian cancer

Endocrine, environmental and genetic factors have been identified in epidemiologic studies to be important in ovarian cancer carcinogenesis. Ovarian cancer is a disease of the elderly population, and most patients are postmenopausal with a median age at diagnosis of approximately 60 years. Other factors associated with ovarian cancer risk include family history, nulliparity, early menarche and late menopause [3]. Multiparity, breast feeding, prolonged use of oral contraceptives [4], and tubal ligation have all been shown to decrease the risk of ovarian cancer [3].

The majority of these tumours arise from epithelial cells covering the surface of the ovary. These cells are organised as a single layer of flat, cuboidal, simple, squamous, epithelial cells with a well-defined basement membrane. The surface epithelial cells of the ovary are derived from mesothelial cells during embryonic development. The epidemiologic data associated with the risk of ovarian cancer have suggested that an accumulated number of menstrual cycles correlates with risk of disease. Each ovulatory cycle ruptures the surface epithelial layer, which requires proliferation and migration of epithelial cells to heal the wound, which frequently results in the formation of deep invaginations or inclusion cysts wherein the surface epithelial cells are now in a different environment. The increased cell proliferation following ovulation is thought to lead to genetic and epigenetic alterations in the surface epithelial cells. Ultimately, sufficient genetic changes are accumulated to produce a malignant transformation and the cells hyperproliferate, disseminate through the peritoneal cavity, and continue to invade and grow within the ovarian cortex. Whereas alternative hypotheses have been generated for the development of ovarian cancer [5,6], this 'incessant ovulation hypothesis' [7] is supported by epidemiologic data linking the risk of ovarian cancer with menstrual cycles [3]. Furthermore, recent laboratory studies by Godwin and colleagues [8] have shown that continuous culturing of rat ovarian surface epithelial cells leads to spontaneous cell transformation, further demonstrating that proliferation of surface epithelial cells is an important aspect of ovarian carcinogenesis.

The development of ovarian cancer is a multistep process that involves alterations in genes which have been classified into three general categories: (1) proto-oncogenes, which stimulate growth; (2) tumour-suppressor genes, whose loss of function gives rise to cancer since they are negative regulators of growth; and (3) DNA repair genes which, when not functioning normally, lead to an increased frequency of non-repair mutations which, in turn, increase the predisposition to cancer. Genes from all three categories have been identified to play a role in ovarian carcinogenesis, although the exact integration and sequence of genic alterations remains to be determined.

Oncogenes associated with signal transduction pathways have been identified to be involved in the pathogenesis of ovarian cancer, and may also be important targets for future molecular therapy. Three such genes are *RAS*, *AKT2*, and *PIK3CA* [9]. The *RAS* family of proto-oncogenes (*H-RAS*, *Ki RAS*, *N-RAS*) encode GTP-binding proteins (termed p21), which have essential roles in cytoplasmic signal transduction pathways. The normal function of p21 is to interact with tyrosine kinase receptors and other proteins to activate signal transduction pathways. Mutations in *RAS* genes are common in numerous cancers. Mutations in the *Ki-RAS* gene appear to be more frequent in ovarian tumours of low malignant potential than in invasive carcinomas.

The *AKT2*-oncogene, a serine-threonine protein kinase, is rapidly activated by mitogenic growth factors through the *PI3*-kinase system, and this increased signalling has been implicated in many processes, such as cell-cycle regulation, cell adhesion, and apoptosis, in which a loss of function or control could contribute to ovarian carcinogenesis [9]. The *AKT2* gene has been shown to be amplified in 12% of ovarian cancers, but no alterations were detected in benign or borderline ovarian tumours [10].

Growth factors and receptors also play an important role in ovarian cancer development. Members of the

growth factor receptor family include the epidermal growth factor receptor (EGF-R) and the oncogene *ERB-B2*. This oncogene has been reported to be overexpressed in approximately 25–30% of human ovarian cancers [11]. Some, but not all, studies have shown a correlation of expression with prognosis [12]. Increased expression of EGF-R has been demonstrated in ovarian carcinoma cell lines and also in tumour tissues. The relationship between EGF-R expression and prognosis remains to be fully defined. However, not only does it appear that growth factors and receptors are important in ovarian oncogenesis, inhibition of the receptors and their associated tyrosine kinase activity may be important therapeutic targets as well.

Godwin and colleagues have recently identified through genetic screens a new candidate oncogene [13]. The synucleins (alpha, beta, gamma and synoretin) are a family of cytoplasmic proteins which are frequently expressed in neurons. Gamma synuclein was expressed in the majority of late-stage carcinomas, but not expressed in normal ovarian surface epithelium [13]. The function of the synucleins remains to be determined. Godwin and colleagues have hypothesised that upregulation of gamma synuclein expression may occur at very early stages of ovarian cancer and that this abnormal expression contributes ultimately to progression and metastatic spread of the disease [9].

Mutations in tumour-suppressor genes have frequently been identified in human cancers. Mutations in p53 are among the most common genetic alterations described thus far in human cancers. In ovarian carcinomas, p53 mutations are present in approximately 30% of human ovarian cancers, and overexpression of the p53 protein has also been observed in about 50% of ovarian cancers [9]. It appears that p53 mutations may occur late in the course of cancer development and progression since p53 mutations were more common in late- than in early-stage ovarian cancer [9]. However, there may be a subset of ovarian cancers where mutation of p53 is an early event since in some cancers an identical pattern of p53 mutation was observed in tumour cells collected from both primary and metastatic sites [9,14,15].

Disabled-2 (*Dab2*) is a candidate ovarian tumour suppressor gene which functions in controlling the position of epithelial cells. Since the hallmark of carcinoma of the ovary is the loss of a continuous basement membrane, this gene may play an important role in initiation and progression. Xu and colleagues [16] have shown that loss of expression of Dab2 is common in ovarian tumours based on immunohistochemical stainings of Dab2, collagen 4, and laminin in premalignant lesions bordering both normal and neoplastic ovarian surface epithelium. They have postulated a series of molecular events are associated with the dysplastic morphological transformation and initiation of ovarian tumorigenicity. In this model, there is transient loss of basement membrane components, such as collagen 4 and laminin, followed by inactivation of the Dab2 oncogene, with subsequent transformation of the epithelial cells followed by a disorganized proliferation of tumour cells [17].

Loss of heterozygosity (LOH) studies were initially used to identify potential tumour-suppressor genes. More sophisticated molecular biological techniques are now being used to identify oncogenes and tumour-suppressor genes. Differential RNA display and microarray analyses are now being used to probe ovarian cancers and normal tissues for gene expression differences [18,19]. The importance of a signal transduction pathway in ovarian oncogenesis has recently been highlighted by the discovery of two other genes involved in this pathway, which are expressed in the normal human ovary, but not in ovarian cancer. Bast and colleagues have reported on the *NOEY2* gene [20], which is analogous to RAS, and appears not to be expressed in the majority of human ovarian cancer cell lines studied. Abdollahi and colleagues [21], using the technique of differential RNA display, demonstrated that the gene *LOT1* showed lost or decreased expression in five of eight independently transformed rat ovarian surface epithelial cell lines compared to normal progenitor ovarian cells. *LOT1* is part of the EGFR signalling pathway and the protein may act as a transcription regulator.

More recently, the powerful new technology of *CDNA* microarray has been used to identify overexpressed genes in ovarian cancer. This technique permits the simultaneous comparison of the expression of thousands of gene samples to identify those that are differentially expressed. This technique will clearly be useful in the molecular classification of tumours as gene expression may correlate with prognosis and response to therapy. In addition, as shown by Mok and colleagues, microarray technology may be used to identify novel molecular markers for ovarian cancer, such as prostasin [22].

3. Hereditary ovarian cancer

About 10% of epithelial ovarian cancer is associated with a germ-line mutation predisposing to ovarian cancer [23,24]. These mutant genes are transmitted in an autosomal dominant manner with variable penetrance. There appear to be at least two distinct manifestations of hereditary ovarian cancer. The breast–ovarian cancer syndrome has been linked to the *BRCA1* gene, and to a lesser extent, to the *BRCA2* gene. The second major hereditary form of ovarian cancer is associated with an excess of colorectal and endometrial cancers, which has defined the hereditary non-polyposis colorectal cancer

(HNPCC) syndrome. *BRCA1* is located on the long arm of chromosome 17 at band q21 and *BRCA2* is located on the long arm of chromosome 13 at band q12-13. Hundreds of mutations have been identified in both of these large genes. It appears that both *BRCA1* and *BRCA2* are involved in transcriptional regulation and DNA repair, although it is possible that these genes may have multiple functions. While there are numerous mutations, only a few of these missense changes have been determined to be associated with an increased risk of disease. The majority of these deleterious mutations are nonsense, splice-site and frameshift (i.e. insertions and deletions) mutations. These lead to truncated forms of the protein and loss of function. It has been estimated that the lifetime risk of a woman with a *BRCA1* alteration to develop ovarian cancer is 15–60% compared to a lifetime risk for the general population of 1.3%. The vast majority of cancer-related *BRCA1* mutations are germ line, whereas somatic mutations are rare in human sporadic ovarian cancers ($<10\%$) [25]. It has been estimated that the proportion of individuals in the general population who carry *BRCA1* mutations is approximately one in 800 [9]. However, the incidence of alterations is as high as 1/40 to 1/50 in the Ashkenazi Jewish population [26]. It is of note that ovarian cancer risk appears to be increased to a lesser degree in women with *BRCA2* mutations than in *BRCA1* mutations with a cumulative risk estimated to be less than 10–20% by age 70 years [9].

The appropriate management for women at high risk for ovarian cancer remains to be determined. Strategies for risk reduction include prophylactic oophorectomy and regular screening with serum CA-125 levels and transvaginal sonography. In addition, in one study, the use of oral contraceptives was associated with a risk reduction of 50–60% in carriers of BRCA mutations [27]. Individuals who undergo prophylactic oophorectomy retain a small risk for the development of peritoneal carcinomatosis. Chemoprevention strategies have also recently been initiated. A randomised prospective trial is in progress by the Gynecologic Oncology Group (GOG), in which women at high risk for ovarian cancer are randomised to immediate prophylactic oophorectomy or 6 months of treatment with fenretinide prior to oophorectomy [28]. This trial was based upon a prior study which revealed that ovaries removed from individuals at high risk for ovarian cancer frequently contain histological features, such as surface epithelial pseudostratification, surface epithelial papillomatosis, deep cortical invaginations of the surface epithelium, epithelial inclusion cysts, and increased stromal activity, which were observed far less frequently and with less intensity than in ovaries from women in the general population [29]. If prospectively validated, such an identifiable premalignant phenotype is a potential useful surrogate endpoint for chemopreventive agents, such as fenretinide.

The HNPCC syndrome is also associated with an increased risk for ovarian cancer. The syndrome is much less common and only counts for 10% of hereditary ovarian cancer. HNPCC syndrome arises from an inherited defect in DNA mismatch repair genes: *hMSH2*, *hMLH1*, *hPMS1*, or *hPMS2*. Mutations in *hMSH2* and *hMLH1* appear to be most frequently associated with ovarian cancer risk in HNPCC syndrome families [9].

There clearly has been a great deal of progress in understanding the genetics of epithelial ovarian cancer. The establishment of the relationship between mutations in *BRCA1* and *BRCA2* genes and inherited predisposition to breast and ovarian cancer has been of major clinical importance. While 90% of ovarian cancer cases are still considered to be sporadic, identification of the molecular events associated with hereditary ovarian cancer will likely lead to an increased understanding of the sporadic disease as well since the two diseases share many clinical features. The development of high-throughput screening methodology, such as cDNA microarray analysis, will lead to the identification of additional genes which are important in the development of ovarian cancer and help define new targets for therapy as well as potential new biomarkers for early detection.

4. Treatment of epithelial ovarian cancer

4.1. The role of surgery

Epithelial ovarian cancer is a surgically staged disease. The components of a comprehensive staging laparotomy should include: (1) a vertical incision extending above the umbilicus; (2) peritoneal washings and/or aspiration of ascites for cytologic analysis; (3) hysterectomy and bilateral salpingo-oophorectomy; (4) pelvic and para-aortic lymph node sampling; (5) diaphragmatic biopsies, particularly the right hemidiaphragm; (6) omentectomy; (7) biopsy of suspicious lesions; and (8) random biopsies through the peritoneum. Such a comprehensive laparotomy is essential since postoperative treatment is based on clinicopathologic features documented at surgery. In addition to accurate staging, the initial laparotomy is important in removing as much disease as possible (cytoreduction). Optimal cytoreduction is considered to have been accomplished when no tumour nodule greater than 1.0 cm remains after surgery. In the United States, patients have frequently been categorised as optimal or sub-optimal based upon this definition and entered on different clinical research protocols designed for these distinct sub-sets of patients. Numerous previous studies have retrospectively demonstrated that the bulk of residual disease after surgery correlates with prognosis [30]. In addition, cytoreduction frequently will relieve symp-

toms associated with a bowel obstruction, even when patients are not optimally cytoreduced.

The true impact of cytoreductive surgery on survival remains controversial. A large retrospective GOG study [31] compared survival of patients with IIIA, IIIB and IIIC disease who were optimally cytoreduced. Patients with IIIA and IIIB by definition did not have bulky upper abdominal disease and, consequently, did not require cytoreduction to achieve an optimal status in the upper abdomen. In contrast, patients with stage IIIC disease by definition had greater than 2.0 cm disease at the time of the operation and required cytoreductive surgery to achieve optimal status. Despite the fact that in this analysis at the conclusion of surgery all patients were considered optimal, patients with stage IIIC disease had inferior survival compared to patients with IIIA and IIIB disease, despite the fact that they were effectively cytoreduced. This demonstrates that biological factors which led to large-volume infiltrative disease in the upper abdomen, even though surgically removable, nevertheless conferred a negative prognostic effect compared to those patients with IIIA and IIIB disease who were diagnosed with small-volume, upper abdominal disease and did not require cytoreduction. Both biological factors as well as surgical resectability are important factors in prognosis.

The timing of cytoreduction also remains a controversy. Cytoreduction at the time of diagnosis is a standard practice, although only approximately 50% of patients can be effectively cytoreduced at the initial laparotomy. In patients in whom the initial cytoreduction was not successful, clinical trials are evaluating the role of interval cytoreduction. Patients with suboptimal disease receive three cycles of chemotherapy, and then if they have a response to treatment, undergo another attempt at cytoreduction followed by additional chemotherapy. A randomised trial of the EORTC demonstrated that interval cytoreduction was superior to chemotherapy alone in patients in whom the initial cytoreduction was not successful [32]. Those patients undergoing interval debulking surgery had a statistically significant improvement, both in time to progression and in median survival (6 months). The GOG has finished accrual to a similar prospective randomised trial of interval debulking surgery, although a different chemotherapeutic regimen was used compared to the EORTC study. Preliminary results from the study should be available in 2002. An alternative approach to initial cytoreduction consists of neoadjuvant chemotherapy in patients with advanced-stage disease. Several non-randomised studies have demonstrated the feasibility of such an approach [33,34]. The EORTC is performing a randomised prospective trial of neoadjuvant chemotherapy versus initial cytoreduction. Interval debulking surgery will be allowed in this trial. Until the conclusion of these clinical trials, cytoreduction as part of the initial laparotomy remains the standard of care in patients with advanced ovarian cancer.

As will be discussed, the majority of patients with advanced ovarian cancer treated with cytoreductive surgery followed by combination chemotherapy will achieve a clinical complete remission defined as absence of symptoms, negative physical examination, no evidence of disease on CT scan, and normalisation of serum CA-125 levels. Second-look laparotomy is a planned surgical procedure in these patients, based upon the hypothesis that the detection of residual disease and subsequent immediate treatment will improve progression-free survival and overall survival. It is clear that approximately 50% of patients who are in a clinical complete remission will have microscopic or macroscopic residual disease detected by a second-look laparotomy. Patients with a negative second-look laparotomy remain at a high risk for recurrence, but have a better overall prognosis than patients who have residual disease identified at second look. However, there is no evidence that treating patients who have a positive second look with any therapeutic modality is superior to the approach of following patients who are in a clinical complete remission and treating them at the time of clinical progression. A second-look laparotomy is not routinely recommended outside of a clinical trial.

Secondary cytoreduction has also been an area of controversy in the management of patients with recurrent disease. Patients with a long disease-free interval and an isolated recurrence without ascites and disseminated carcinomatosis may benefit from secondary debulking, in particular if it appears that the patient will have a reasonable chance of responding to additional chemotherapy. As the primary morbidity from ovarian cancer is the development of bowel obstruction, surgery is an essential part of management of patients in the palliative stages of their illness.

4.2. *Prognostic factors*

Clinical prognostic factors have been well defined in ovarian cancer and include the stage of the disease, volume of the disease before and after surgery, grade of the tumour or degree of differentiation, histology, performance status, and age [35]. In addition, serum CA-125 levels have been correlated with prognosis. At the time of diagnosis, CA-125 levels are linked to volume of disease. Monitoring of serum CA-125 levels during chemotherapy has also been shown to be prognostically important. Failure of tumour markers to normalise following three cycles of chemotherapy is associated with the markedly decreased likelihood of achieving a complete remission and with an adverse long-term prognosis. Serum CA-125 levels are also monitored following achievement of a complete remission. Eleva-

tions in CA-125 levels after completion of chemotherapy are predictive for a clinical relapse with a median time of 4–6 months. Management of patients who have only an elevation in CA-125 levels following chemotherapy and who remain asymptomatic and have no physical findings or radiographic findings of disease remains an area of controversy. There is no evidence that immediate chemotherapy is beneficial in this group of patients and tamoxifen is frequently recommended. A prospective trial is currently in progress in England to determine whether immediate chemotherapy for a rising CA-125 level is superior to a policy of observation until patients develop clinically manifest disease.

More recently, numerous biologic prognostic factors [12] have also been identified and include abnormalities in genes associated with signal transduction, apoptosis, drug resistance, angiogenesis, metastases, and cytokine levels. When such molecular abnormalities have not routinely been used to help select specific therapies for individual patients with ovarian cancer, they have identified new potential molecular targets, and clinical trials of targeted molecular therapy have been initiated and will be subsequently described.

4.3. Management of early-stage ovarian cancer

The appropriate management of patients with FIGO stages I and II has been an area of controversy. In contrast to patients with advanced-stage disease where a series of clinical trials have been performed which have helped define optimal therapy, clinical trials in patients with early-stage disease have not yet provided a consensus for optimum therapy. This relates to the fact that only 20% of patients with ovarian cancer are diagnosed with early-stage disease, the lack of uniform staging for all patients entered on clinical trials, and the relatively favourable prognosis of this group of patients, which requires long follow-up before the results of any therapeutic intervention can be assessed. The components of a comprehensive staging laparotomy have previously been defined, but it appears that only a minority of patients with disease clinically felt to be confined to the pelvis actually undergo all the required procedures for a comprehensive staging laparotomy. It has been established that patients with stage IA or IB disease with grade 1 or grade 2 tumours after a comprehensive laparotomy have a greater than 90% cure rate with surgery alone and, consequently, no adjuvant therapies are recommended for this group of patients [36]. In contrast, patients with high-risk early-stage ovarian cancer (operationally defined as stage II, stage IA or IB with grade 3 tumours, stage IC disease, or clear cell carcinomas) have a recurrence rate of 30–40%, depending upon individual risk factors. Recently, Vergote and colleagues [37] reported the results of a multivariate analysis of 1000 patients with early-stage disease and established the four most important risk factors: degree of differentiation, FIGO stage IA or IB, rupture of the capsule, and age. In GOG studies, high-risk patients have been treated on a series of prospective trials evaluating the role of intraperitoneal p32, cisplatin and cyclophosphamide, and recently with paclitaxel plus carboplatin combinations. In Europe, the ICON Clinical Trials Group and the EORTC Action Group have explored a strategy of delaying treatment for high-risk individuals until recurrence. In the Action trial, it was required that patients undergo comprehensive staging laparotomy before being randomised to immediate chemotherapy or chemotherapy at the time of recurrence. In the ICON study, patients were not required to undergo comprehensive staging laparotomy and the primary eligibility criteria for the study was the physician's belief that the patient may benefit from chemotherapy and had early-stage disease. These patients were not comprehensively staged, but were randomised in the same manner as the Action study. The results of these two studies were pooled and there was a 7% improvement in survival for patients treated with immediate chemotherapy compared to a strategy of treating patients only when they recurred [38]. It has been argued that the chemotherapy was basically treating those patients who did not have a comprehensive laparotomy and, in fact, had undetected metastatic disease. This would include most of the patients on the ICON Study and, even though the Action Study required comprehensive staging, it was apparent after review of the operative notes that a significant fraction of patients on this study also were not accurately staged. Consequently, there still is debate as to whether comprehensively staged patients benefit from chemotherapy. Nevertheless, in the United States, postoperative chemotherapy has become the standard of care for patients with early-stage ovarian cancer. In the current GOG protocol, patients with high-risk early-stage disease receive three cycles of paclitaxel plus carboplatin and are randomised to receive an additional 24 weekly administrations of paclitaxel or to observation. The low-dose paclitaxel in this protocol is being administered with the rationale that it may have antiangiogenic effects. A previous GOG study randomised patients with early-stage high-risk disease to three versus six cycles of paclitaxel plus carboplatin at standard doses, and the results of that study should be available this year. It appears that a study to establish chemotherapy benefit in meticulously staged ovarian cancer patients may not be possible due to the small number of patients and to the fact that, despite guidelines for comprehensive staging laparotomy which have been widely disseminated, many patients still do not undergo such a procedure. It remains a matter of debate whether patients who are inadequately staged, but felt to have early-stage ovarian cancer, should undergo a compre-

hensive staging laparotomy to accurately determine their true stage.

5. Chemotherapy for advanced-stage ovarian cancer

5.1. Induction chemotherapy

Ovarian cancer is a chemosensitive disease and numerous cytotoxic agents have been shown to produce a greater than 20% objective response rate as single agents. Included in this group are alkylating agents, antimetabolites, platinum complexes, anthracyclines, and taxanes. A series of prospective randomised trials of a variety of combinations and single agents were performed in the 1970s and 1980s Table 1 [39–41]. The results of these clinical trials were reviewed and, on the basis of meta-analysis, certain conclusions were drawn: (1) platinum-based chemotherapy was superior to non-platinum-based chemotherapy; (2) anthracyclines increased survival by 7% compared to treatment regimens which did not include anthracyclines; (3) there was a slight advantage for platinum-based combinations compared to treatment with single-agent platinum; and (4) carboplatin and cisplatin produced equivalent results with regard to survival. These results demonstrated that platinum compounds were the single most active agents in ovarian cancer. With a subsequent demonstration that taxanes had a high degree of activity in patients with recurrent ovarian cancer [42,43], a series of recent randomised trials have been performed which have now established a new standard of care for patients with advanced ovarian cancer. The addition of paclitaxel to platinum in GOG 111 for the first time demonstrated that survival of patients with suboptimal stage III and IV disease could be improved compared to treatment with cisplatin plus cyclophosphamide [44]. In this pivotal randomised trial, patients treated with the paclitaxel-based combination had a 4-month improvement to progression-free survival and a 14-month improvement in median survival. The study was performed without significant crossover for those patients who were initially randomised to cisplatin plus cyclophosphamide since paclitaxel was not routinely available. The results of GOG 111 were confirmed by a separate randomised trial (OV 10) performed by European and Canadian investigators, which also demonstrated a survival advantage for patients initially randomised to paclitaxel plus cisplatin [45].

A subsequent trial by the GOG [46] compared treatment with single-agent cisplatin or single-agent paclitaxel to the combination of the two drugs in previously untreated patients with suboptimal stage III and IV disease (GOG 132). In this trial, there was no overall difference in survival. Virtually all patients initially randomised to single-agent cisplatin or paclitaxel essentially received both drugs in sequence and frequently were treated for a longer period of time than those patients initially randomised to receive the combination of paclitaxel and cisplatin. Consequently, based on the decreased toxicity, the GOG continued to recommend combination therapy with cisplatin plus paclitaxel as the standard regimen to compare against new combinations.

The ICON 3 trial [47] randomised patients with stages I through IV ovarian cancer to treatment with paclitaxel plus carboplatin compared with standard therapy. In this trial, standard therapy was based on the investigators' choice of carboplatin or the three-drug combination of cisplatin plus adriamycin plus cyclophosphamide (PAC). Thus, this study was actually two trials combined into one, and the heterogeneous group of patients has caused some investigators to question the conclusion that there is no clinical benefit for patients treated with carboplatin plus paclitaxel compared with prior standard regimens.

Based in part on the meta-analyses reporting the benefit of adriamycin, the ICON 2 trial randomised patients with advanced ovarian cancer to treatment with single-agent carboplatin or the three-drug PAC combination [48]. In over 1500 patients, there was no significant improvement in survival for patients treated with a three-drug regimen. Taken as a group, these studies demonstrated the importance of platinum in the

Table 1
Pivotal chemotherapy trials in ovarian cancer

Trial	Result	Ref.
GOG 111: Cisplatin + cyclophosphamide versus cisplatin + paclitaxel	Improved PFS (14 months versus 18 months) and median survival (24 months versus 38 months) for paclitaxel combination	
GOG 158: Cisplatin + paclitaxel versus carboplatin + paclitaxel	Risk of progression lower for carboplatin + paclitaxel and less toxicity than cisplatin + paclitaxel	
EORTC/ACTION: Observation versus chemotherapy in early-stage disease	7% improvement in 5-year survival for immediate chemotherapy	

chemotherapy of patients with advanced ovarian cancer and that paclitaxel produced an added benefit, although the extent of that benefit remains an area of some debate, particularly outside the United States.

Three subsequent studies [49–51] compared cisplatin plus paclitaxel versus the carboplatin plus paclitaxel combination [52]. The rationale for these studies was that carboplatin is a much less toxic platinum analogue and, in particular, could be combined easily with paclitaxel in a 3-h infusion compared to the 24-h infusion which was used in GOG 111 when paclitaxel was administered together with cisplatin. All three randomised trials came to the same conclusion that carboplatin plus paclitaxel was equally effective and less toxic than the cisplatin plus paclitaxel combination. The largest of these trials was GOG 158 [51] in which 800 patients with optimal stage III ovarian cancer were randomised to cisplatin (75 mg/m^2) plus paclitaxel (135 mg/m^2 in a 24-h infusion) or to carboplatin Area Under the Curve (AUC = 7.5) together with paclitaxel (175 mg/m^2 in a 3-h infusion). Patients received six courses which were 21 days in length. This trial was based on earlier concerns that carboplatin may be less effective than cisplatin in patients with potentially curable ovarian cancer (optimal stage III disease) and to the fact that a 24-h infusion of paclitaxel may be superior to a 3-h infusion. However, in GOG 158, the risk of progression (0.86) favoured the carboplatin/paclitaxel regimen compared with the cisplatin/paclitaxel combination. In addition to a decreased risk of progression, the carboplatin plus paclitaxel combination was associated with significantly less toxicity, primarily related to the well-known cisplatin toxicities, such as nausea, vomiting and nephrotoxicity. The study also pointed out the limitations as to what can be expected with current chemotherapy in patients with advanced-stage ovarian cancer: the median disease-free survival was 22 months, even in this group of patients with optimal stage III disease. However, overall median survival would be greater than 4 years, which again demonstrates that this disease can be managed for long periods of time, even after patients relapse following initial chemotherapy.

The optimum carboplatin dose remains to be defined when using combination chemotherapy with a taxane. In the GOG study, as noted, patients received an AUC of 7.5, which was higher than the other randomised trials [49,50] comparing carboplatin plus paclitaxel versus cisplatin plus paclitaxel. In contrast to the GOG trial, the other two studies reported a risk of failure for the carboplatin regimen which was slightly greater than 1.0, although not statistically significant. Outside of a randomised trial, it is not possible to conclude that an AUC of 7.5 is superior to an AUC of 5.0–6.0, which has been used in other trials. It is reasonable to start patients at an AUC of 7.5, but there is no evidence that maintaining such a dose is necessary if substantial toxicity exists and dose reductions are recommended. There is no evidence that the dose of paclitaxel should be increased. A recent trial from Italy [53] randomised patients to two different doses of paclitaxel (175 mg/m^2 versus 225 mg/m^2) with outpatients receiving the same AUC of carboplatin (6.0). There was no difference in survival in this trial and 175 mg/m^2 for a 3-h infusion remains the optimum dose of paclitaxel when combined with carboplatin.

Docetaxel, a taxane analogue, which in experimental systems has been shown to be more interactive than paclitaxel, has also been shown to be an active agent in recurrent ovarian cancer. The SCOTROC [54] investigators performed a large randomised trial comparing docetaxel (75 mg/m^2 in a 1-h infusion) and carboplatin at an AUC of 6.0 versus paclitaxel (175 mg/m^2 in a 3-h infusion) plus carboplatin at an AUC of 6.0 in previously untreated patients with advanced ovarian cancer. This study was initially powered as a superiority study. However, preliminary results suggest there will be no significant difference in efficacy for these two taxanes when combined with carboplatin as the initial disease-free intervals were essentially identical. There was, however, a substantial difference in toxicity between these two combinations. The docetaxel-treated patients had more myelosuppressive complications, such as neutropenic fevers, prolonged episodes of grade 4 neutropenia, the necessity of antibiotics, and the use of G-CSF. In contrast, the paclitaxel combination was associated with peripheral neuropathy, which led to a substantial rate of treatment discontinuation which was not observed in the other randomised trials of carboplatin plus paclitaxel. These results demonstrated that docetaxel plus carboplatin can be considered an acceptable alternative to the more standard use of carboplatin plus paclitaxel.

5.2. Intraperitoneal chemotherapy

The morbidity of ovarian cancer primarily relates to peritoneal carcinomatosis. Consequently, the direct administration of chemotherapeutic agents into the intraperitoneal cavity has been extensively evaluated. In the most recent randomised trial (GOG 114) [55], patients with optimal stage III disease received six cycles of cisplatin plus paclitaxel with both drugs given intravenously or to an experimental regimen which consisted of two cycles of high-dose carboplatin (AUC = 9.0) followed by six cycles of intraperitoneal cisplatin (100 mg/m^2 together with paclitaxel 135 mg/m^2 in a 24-h infusion). The intraperitoneal regimen produced a statistically significant improvement in disease-free survival with a borderline improvement in overall survival. However, excess toxicity in the experimental arm, particularly grade 4 neutropenia, has not led to a further evaluation of this particular regimen. The GOG has

completed a subsequent trial in optimal stage III patients in which the control arm was once again intravenous cisplatin/paclitaxel and the experimental arm was a regimen consisting of intraperitoneal cisplatin and paclitaxel as well as intravenous paclitaxel. Accrual has been completed; however, no results are yet available from this study. The GOG currently is not performing any further randomised trials of intraperitoneal chemotherapy. Most investigators consider the intraperitoneal route as investigational and do not routinely recommend such treatment outside the confines of a clinical trial.

5.3. High-dose chemotherapy

Based on retrospective studies which have suggested a relationship between survival and dose intensity of chemotherapeutic agents used in ovarian cancer, prospective trials have explored high-dose therapy in patients with ovarian cancer. Phase II trials of high-dose chemotherapy with peripheral stem-cell transfusion have suggested a high response rate and longer disease-free survival than could be achieved with standard doses [56]. However, no phase III randomised trials have been completed in the United States. In European registry studies, outcomes associated with high-dose chemotherapy and hematologic support in advanced ovarian cancer patients have produced disease-free survival and overall survival which appear to be similar to that which can be observed with standard doses in GOG trials [57]. In addition, a series of prospective randomised trials comparing different doses of cisplatin as well as different AUCs of carboplatin have failed to demonstrate an improvement in overall survival for the higher dose therapy. Consequently, it does not appear the dose–response relationship with platinum compounds is of such a magnitude that it provides a clinical advantage for high-dose chemotherapy which requires stem-cell support. In the Gynecology Oncology Group, there are no prospective randomised trials comparing high-dose chemotherapy with autologous transplantation, although European trials are still in progress.

5.4. Maintenance therapy

As previously noted, the majority of patients with advanced ovarian cancer achieve a clinical complete remission following six cycles of paclitaxel plus carboplatin after initial cytoreductive surgery. Unfortunately, at least 50% of patients in a clinical complete remission will ultimately recur. Clinical trials are currently in progress exploring the role of maintenance therapy in patients who do achieve a clinical complete remission. The GOG/SWOG trial randomised patients to 3 versus 12 months of standard paclitaxel administered at an initial dose of 175 mg/m^2 in a 3-h infusion. This study has recently been closed by the Data Safety Monitoring Board due to superior progression-free survival for patients with the 12 cycles of treatment [58]. No survival data, however, are available from this trial. A similar trial has been performed in Italy with a randomization to observation versus every 3-week paclitaxel, but there also are no results available from this trial. French investigators reported the preliminary results of a randomised trial of high-dose chemotherapy with stem-cell transplantation compared to maintenance therapy with standard doses of traditional cytotoxic agents [59]. Superior disease-free interval was observed for the high-dose chemotherapy regimen in a subset of patients with drug-sensitive small-volume disease. Another strategy has been to use immunotherapy in patients who achieve a clinical complete remission. A randomised trial has been formed with an antibody against CA-125 versus placebo, although no survival data are yet available from this study [60]. At this point, the benefit of maintenance therapy remains to be completely established. The SWOG data are of interest; however, similar observations have been observed in other tumours, such as breast cancer, where progression-free survival was improved by continuation of therapy without any impact on overall survival.

5.5. New chemotherapy regimens

Phase II trials in platinum-resistant patients have identified the activity of numerous agents, including topotecan, gemcitabine, oral VP-16, encapsulated doxorubicin, and docetaxel [61,62]. These agents have been combined with platinum compounds and paclitaxel in phase II studies, which have now been followed by prospective randomised comparisons. As noted, the SCOTROC trial of carboplatin plus paclitaxel versus docetaxel plus carboplatin failed to demonstrate any significant improvement in disease-free survival. The three-drug combination of carboplatin, paclitaxel and gemcitabine has been studied in a phase II trial of previously untreated patients with advanced ovarian cancer. Hansen and colleagues [63] reported this combination produced an objective response rate of 100% in the first 24 previously untreated patients with advanced ovarian cancer. Larger phase II trials of this combination are in progress in Europe. Other investigators have evaluated sequential doublets with cisplatin plus topotecan followed by cisplatin plus paclitaxel. In a phase II trial of previously untreated patients, they reported a high response rate (78%); however, this was associated with significant myelosuppression [64].

Another group of investigators has evaluated a three-drug combination of paclitaxel plus epirubicin plus carboplatin (TEC) based on encouraging phase II trials. However, the randomised phase III trial [65] demon-

strated that the TEC combination could be administered at full doses, although there was no apparent advantage for time to progression. These investigators continue to use carboplatin plus paclitaxel as the standard regimen.

GOG 182 is the largest prospective randomised trial ever performed in previously untreated patients with advanced ovarian cancer. This study has now become an international trial with patients being entered in Europe, Canada, Australia and New Zealand. The outline of GOG 182 is summarised in Table 2 [66]. The control arm consists of eight cycles of carboplatin plus paclitaxel. There are two triplets being studied: paclitaxel plus carboplatin plus gemcitabine and paclitaxel plus carboplatin plus encapsulated doxorubicin. There are also two sequential doublets: carboplatin plus topotecan for four cycles followed by paclitaxel plus carboplatin for four cycles, or gemcitabine plus carboplatin for four cycles followed by paclitaxel plus carboplatin for four cycles. This last treatment arm will also serve as a comparison to the triplet therapy in which the same two drugs are used in combination.

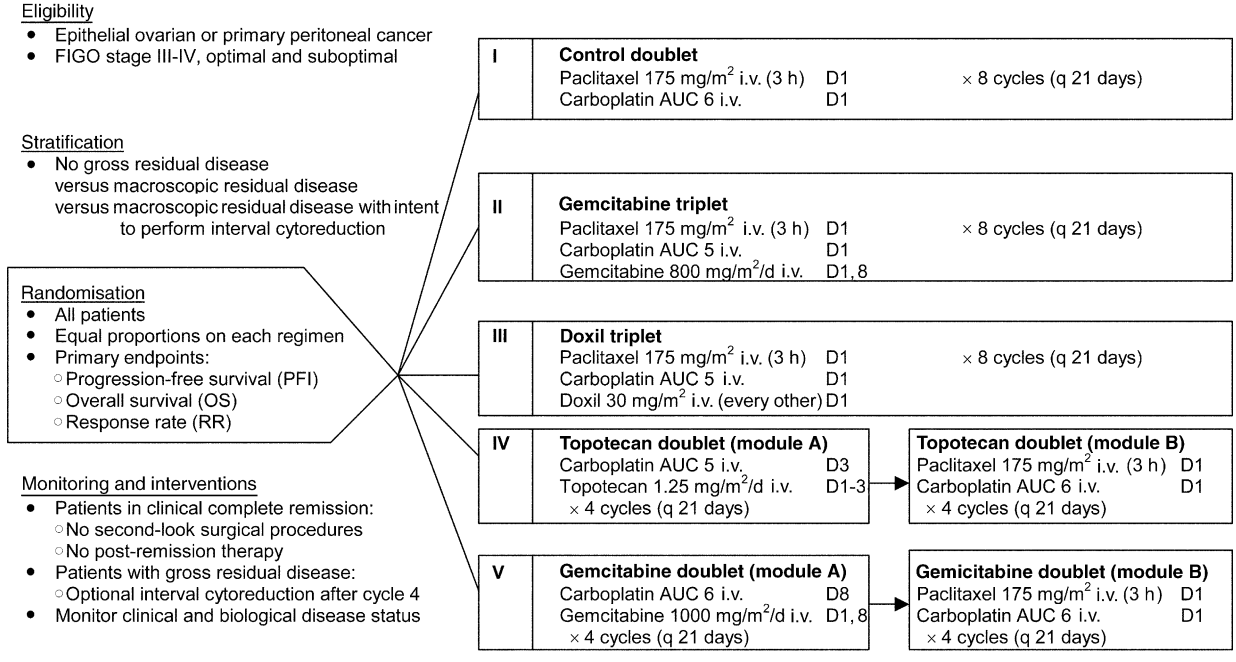
A group of European investigators are randomising patients to paclitaxel plus carboplatin versus paclitaxel plus carboplatin plus gemcitabine since they had concerns that the five-arm study may have difficulty in accruing patients. However, at this point, GOG 182 is accruing at a rapid rate and should have interim analysis in 2 years. These randomised trials will determine whether three-drug combinations can improve outcomes compared to treatment with carboplatin plus paclitaxel.

5.6. Future studies in ovarian cancer

As previously described, the increased understanding of ovarian carcinogenesis has led to new potential targets for therapy. The epidermal growth factor receptor complex has been the target for monoclonal antibodies, such as C225, as well as small molecules which interfere with the ATP binding site of the receptor-associated tyrosine kinase (OSI 774, ZD 1839). In phase I/II studies with OSI 774 [67], responses have been observed, and ZD 1839 has entered a phase II trial in GOG patients with recurrent ovarian cancer [68]. Agents which interfere with angiogenesis or inhibit matrix metalloproteinases are also undergoing clinical evaluation in ovarian cancer. In addition to antibodies against CA-125, as previously described, other vaccines are being studied, primarily in patients who achieve a clinical complete remission.

It is likely that chemotherapy will continue to have a major role in the treatment of patients with advanced ovarian cancer. Molecular targeted agents have a synergistic effect with chemotherapy and they are likely to have the greatest benefit in patients who have small-volume disease. As previously noted, most patients with ovarian cancer can achieve a small-volume disease

Table 2
Schema for GOG 182: a phase III randomised trial of paclitaxel and carboplatin versus triplet or sequential doublet combinations in patients with epithelial ovarian or primary peritoneal carcinoma



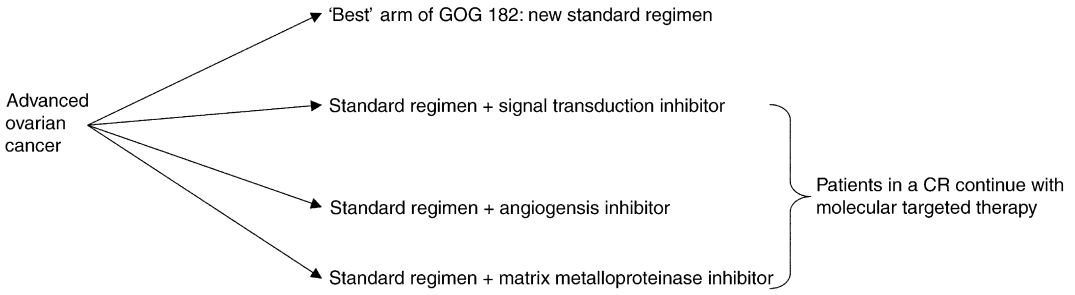


Fig. 1. Possible future clinical trials in ovarian cancer.

status and, consequently, ovarian cancer is perhaps a prototype model in which molecular-targeted therapies may have a role. The previously described prospective randomised trials will establish what is the optimum chemotherapy regimen for patients with advanced ovarian cancer. Subsequent trials will combine chemotherapy together with molecular-targeted biological agents as initial therapy for patients with advanced ovarian cancer. It is probable also that maintenance therapy with vaccines or molecular targeted therapies will continue after chemotherapy is discontinued after a defined number of cycles in an effort to prevent or delay recurrences. Such a new paradigm of treatment will need to be validated in prospective randomised trials. (Fig. 1)

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