Current management of ovarian carcinoma

Epithelial ovarian cancer is a common gynecologic malignancy with an increasing incidence possibly due to the spread of ‘Westernized’ lifestyles. Currently most women present at an advanced stage, and despite radical surgery and chemotherapy, will eventually die from their disease. This article aims to review current surgical and medical management of women with ovarian cancer and the evidence which supports it. Finally, there will be a brief discussion of some of the novel therapies in development.

Ovarian cancer is the leading cause of mortality in gynecologic oncology in the developed world, with an estimated 6500 cases annually in the UK [1]. The majority of women (approximately 75%) will present with disease already spread beyond the pelvis (Federation Internationale de Gynecologie et d’Obstetrique [FIGO] Stage III and IV) [2], which has an associated 5-year survival of 21% [3]. Ovarian cancer accounts for more deaths than all of the other gynecologic cancers combined. Whilst there are a wide variety of histologic subtypes, over 90% are of epithelial origin, and shall be the focus of this review (Table 1). Epithelial ovarian cancer is primarily a disease of postmenopausal women with a peak incidence of 63 years. The lifetime risk is approximately 1:50, with an incidence of 15/100,000 women/year in the UK [1].

Presentation/clinical symptoms
The clinical presentation for this disease varies, with nonspecific symptomatology making an accurate diagnosis in the primary care setting difficult. Because of the nonspecific symptoms, up to 50% of women will be initially referred to a specialist other than a gynecologist [4]. In 10% of cases the disease is found incidentally in the absence of obvious symptoms. The main associated symptoms include: abdominal swelling and pain; unexplained weight loss or gain; anorexia and nausea; bowel disturbance – urinary frequency or urgency; dyspareunia; menstrual irregularity or postmenopausal bleeding; venous thromboembolism, and dyspnoea. Symptoms are classically of short duration – 6 to 12 weeks [4]. However, a recent study of women with ovarian cancer suggested that prediagnostic symptoms have a longer duration than previously thought [5]. The symptoms were vague, generalized and commonly occur in matched controls, but the combination of unrelated symptoms was more common in cancer cases and should prompt appropriate investigations for ovarian cancer.

Diagnosis
Histologic confirmation is required for diagnosis. Normally this is achieved at primary surgery, although the use of radiologically directed biopsy is increasing for those women with suspected advanced disease. Prior to surgery, the risk of malignancy in a woman with an ovarian mass can be estimated. Features of pelvic ultrasound findings – age and serum CA125 – are used in the calculation of risk of malignancy (RMI), which can be used to ensure those patients with a high risk are managed by specifically trained specialists which can improve outcome [6,7]. However, the investigations are not diagnostic and CA125 can be elevated in many other conditions such as pregnancy, cardiac failure, postsurgical intervention and endometriosis.

Treatment
The role of surgery
A laparotomy is still deemed the ‘gold standard’ primary intervention in suspected ovarian malignancy. The objectives of surgery are to diagnose, stage and excise all macroscopic disease. This usually entails hysterectomy, bilateral salpingo-oophorectomy, omentectomy, retroperitoneal lymph node sampling/dissection, and peritoneal washings/ascitic fluid collection for cytological evaluation. Not all of these procedures are required in every woman, although adequate sampling for staging is necessary [2]. In the younger woman with a suspicious ovarian mass where fertility preservation is an issue, initial surgery should aim to diagnose and stage so that appropriate further management can be instigated.
Germ cell tumors are much more common in younger women. These are frequently sensitive to chemotherapeutic agents and so fertility sparing surgery may be an option [8].

**Primary debulking surgery**

Staging in ovarian cancer is by the FIGO classification (Table 2). In early stage disease (FIGO Stage I–IIA), radical surgery will cure most women, although evidence from randomized control trials suggests that some women (in particular if not optimally stage) with early stage disease would benefit from adjuvant cytotoxic agents [9]. Unfortunately, even with these trials there are still limitations in identifying exactly those who clearly benefit from chemotherapy, although advances in elucidating genetic signatures of individual cancers may make this possible in the future [10].

In advanced disease (FIGO Stage III–IVC), where all macroscopic disease cannot be excised, the practice for many decades has been to debulk the tumor, aiming to excise as much as possible (maximal cytoreductive surgery). The definition of ‘optimal debulking’ has changed with improvements in surgical technology and anesthetic care and the aim now is to leave no macroscopic disease. The origins of this approach commenced with the publication of a retrospective series of 102 women, in which univariate analysis revealed a better survival pattern for those in whom no residual tumor mass greater than that 1.6 cm in diameter remained [11]. The conclusion was that ‘surgery provides optimum benefit when all gross tumor can be excised safely’. Subsequently, a small prospective series by the same group (n = 26) suggested that achieving this ‘optimum’ debulking was the cause of the improved outcome [12]. However, this remains the only evidence supporting this theory, although many papers over the years do indicate that optimum debulking is an independent prognosticator for ovarian cancer. Nevertheless, without randomized trials, the question as to whether achieving debulking is a surrogate of inherent tumor biology, and possibly chemosensitivity, will remain unanswered. Meta-analyses of the nonrandomized prospective and retrospective trials of the effect of surgery have been performed, all with their limitations [13,14](Table 3).

However without the results of randomized control trials it is impossible to control for the effect of tumor biology on surgical resectability. Recently there has been a growing trend to treat advanced ovarian cancer with chemotherapy first and then to perform surgery. The theory for this approach is that women with disease which is unlikely to be maximally debulked at primary surgery may be more likely to have

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**Table 1. Histologic subtypes of ovarian cancer.**

<table>
<thead>
<tr>
<th>Subtype</th>
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<tbody>
<tr>
<td><strong>Epithelial</strong></td>
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<tr>
<td>Serous cystadenocarcinoma</td>
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<td>Mucinous cystadenocarcinoma</td>
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<tr>
<td>Endometrioid adenocarcinoma</td>
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<tr>
<td>Clear cell</td>
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<tr>
<td>Undifferentiated</td>
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<tr>
<td><strong>Sex cord-stromal</strong></td>
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<tr>
<td>Granulosa-stromal cell tumors</td>
</tr>
<tr>
<td>• Granuloma cell</td>
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<tr>
<td>• Thecoma</td>
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<tr>
<td>• Fibroma</td>
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<tr>
<td><strong>Androblastomas</strong></td>
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<td>• Sertoli cell</td>
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<td>• Sertoli-Leidig cell</td>
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<td>• Leidig cell</td>
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<tr>
<td><strong>Germ cell</strong></td>
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<tr>
<td>Dysgerminoma</td>
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<tr>
<td><strong>Embryonal carcinoma</strong></td>
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<tr>
<td>• Embryonic:</td>
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<tr>
<td>• Immature teratoma</td>
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<tr>
<td>• Mature teratoma</td>
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<tr>
<td>• Stroma ovarii</td>
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<tr>
<td>• Carcinoid</td>
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<tr>
<td>• Extra embryonic:</td>
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<tr>
<td>• Endodermal sinus tumor (yolk sac)</td>
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<tr>
<td>• Choriocarcinoma</td>
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<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Lipoid cell tumor</td>
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<tr>
<td>Sarcoma</td>
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<tr>
<td>Small-cell carcinoma</td>
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<tr>
<td><strong>Metastatic tumor</strong></td>
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<tr>
<td>• Gynecologic:</td>
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<tr>
<td>• Tubal</td>
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<tr>
<td>• Endometrial</td>
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<tr>
<td>• Cervical</td>
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<tr>
<td>• Nongynecologic:</td>
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<tr>
<td>• Breast</td>
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<tr>
<td>• Stomach</td>
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<tr>
<td>• Colon</td>
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<tr>
<td>• Lymphoma</td>
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<td>• Melanoma</td>
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<tr>
<td>• Carcinoid</td>
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</table>

Germ cell tumors are much more common in younger women. These are frequently sensitive to chemotherapeutic agents and so fertility sparing surgery may be an option [8].
optimal surgery following chemotherapy when the volume of disease may have been considerably reduced. However, evidence to support this is limited to nonrandomized trials and the effect of patient selection needs addressing.

To address the role of primary debulking surgery in advanced ovarian cancer requires prospective randomized trials. Two such studies are currently recruiting: the Gynaecological Cancer Cooperative of the European Organization for Research and Treatment of Cancer (EORTC) and CHEmotherapy OR Upfront Surgery (CHORUS – Royal College of Obstetricians and Gynaecologists/RCOG)/Medical Research Council, UK) [15]. In both studies, one arm has the surgical debulking effort during, rather than prior to, chemotherapy (Figure 1). Arguably, in order to truly determine whether surgery is effective, one arm should not include surgery. However, this was deemed a step too far at the time of protocol development. Nevertheless, depending on the results of these trials, it may be that such a study would be the next logical question.

**Interval debulking surgery**

Whilst the answer of primary debulking surgery presently eludes us, there is some evidence for its use in other situations. The EORTC study was a randomized trial to assess the effect of interval debulking surgery during adjuvant chemotherapy [16]. Women were eligible if they had

- Biopsy-proven epithelial ovarian cancer FIGO Stage II–IVb
- Residual disease of 1 cm diameter or more following primary surgery
- A tumor which showed response to three cycles of cisplatin/cyclophosphamide chemotherapy (complete response, partial response or stable disease)

Women who were randomized to a second laparotomy had an increased median overall survival of 6 months (p = 0.01). As a result, this approach became popular across Europe. However, a further study of 425 women from the Gynecologic Oncology Group (GOG 152) in the USA, demonstrated no difference in median survival between interval debulking surgery and no surgery (32 vs. 33 months respectively) [17]. It is possible that these studies are not comparable, as in GOG 152 women received both paclitaxel and cisplatin, whereas in the EORTC study paclitaxel was not administered, with the GOG patients having surgery by trained Gynecologic Oncologists in all cases. For the advocates of debulking, the EORTC study does reveal some interesting findings in the arm where a second operation was performed:

<table>
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<tr>
<th>Table 2. FIGO staging of ovarian cancer.</th>
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<td><strong>Stage</strong></td>
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<td>Stage I</td>
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<tr>
<td>a</td>
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<td>Stage II</td>
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<td>Stage III</td>
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<tr>
<td>Stage IV</td>
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**FIGO: Federation Internationale de Gynecologie et d’Obstetrique.**

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<table>
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<th>Table 3. Meta-analysis of trials for primary cytoreductive surgery (nonrandomized control trials).</th>
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<td><strong>Study</strong></td>
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<tr>
<td>-----------------------------------------------</td>
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<tr>
<td>Bristow et al. (2002)</td>
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<td>Hunter et al. (1992)</td>
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<td>Allen et al. (1995)</td>
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CI: Confidence interval. Residual tumor masses < 2 cm in diameter.
• In a third of women, further surgical excision was not feasible
• In a third of women there had been a complete response
• The remaining third showed no macroscopic disease

Assuming that cytoreduction achieves longer survival, it is likely that a small proportion of women significantly influenced the overall survival.

Second-look surgery
Second-look laparotomy was part of routine management in the 1960s and 70s when long-term adjuvant chemotherapy was employed. Second-look laparotomy was performed to determine whether further chemotherapy was necessary, or if it could be safely stopped in order to avoid development of iatrogenic malignancies [18,19]. This surgery was normally performed after 12 months of adjuvant therapy. However, without evaluation this then became part of standard practice, even with developments in cytotoxic agents and sophisticated imaging techniques. The only randomized control trial to address the worth of second-look laparotomy revealed no survival benefit [20]. Advances in laparoscopic techniques have led to renewed interest in second-look surgery to evaluate disease. In a series of 150 clinically disease-free women who underwent a second-look laparoscopy after chemotherapy, 54% had pathologic evidence of disease. Conversion to laparotomy occurred in 12% of cases and 2.7% had a major complication [21]. Whether any of these women benefited in terms of survival or psychological wellbeing remains to be proven. Currently, the evidence to support debulking surgery at the time of second-look surgery is conflicting, for what is essentially persistent disease [20,22–24]. Therefore second-look surgery should be restricted to clinical trials and for carefully selected patients with symptomatic disease with the hope of providing palliation.

Surgery at relapse
Unfortunately, despite high response rates to primary chemotherapy, most women with advanced disease at presentation will relapse and die of their disease. Relapsed disease is defined as proven disease identified more than 6 months after primary chemotherapy to which there was a complete response with evidence of disease prior to this deemed persistent. Surgery may be able to provide palliation of pressure symptoms, if caused by a large tumor mass. However, evidence for any beneficial effect on survival is scarce. There are no prospective studies on the role of surgery after relapse. Nevertheless, a number of retrospective and prospective case series have indicated that there is a cohort of women for whom a second operation may be beneficial (Table 4) [25–29]. However, the problem of elucidating whether this is due to the effect of surgery or inherent tumor biology, as with primary surgery, remains. Survival was more likely if the patient had a good performance status, had not received salvage chemotherapy prior to surgery and did not have a brief disease-free interval following primary treatment [27]. Attempts have been made to evaluate the role of surgery at relapse with randomized control trials, but lack of recruitment lead to the trials being abandoned.

The role of chemotherapy
Primary treatment
Platinum agents
Current first-line medical management of ovarian cancer centers on the alkylating platinum agents, cisplatin and carboplatin. Cisplatin for ovarian cancer was first introduced in the 1970s and achieved response rates of up to 50% in relapsed disease, previously treated with adjuvant chemotherapy [30,31].® Responses to the cisplatin analog, carboplatin, were demonstrated in heavily pretreated relapsed
patients, but with less severe side-effects, and it was mooted as a less toxic alternative to cisplatin as early as 1982 [32]. In a small randomized trial of single-agent cisplatin versus cyclophosphamide, as first-line medical treatment in ovarian cancer, cisplatin gave an improved median survival of 19 months compared with 12 [33]. Further supporting evidence for the role of platinum drugs in first-line medical treatment of ovarian cancer came from a meta-analysis by the Advanced Ovarian Cancer Trialists Group (AOCTG). They reanalyzed individual data from 8139 women included in 45 different trials. The results did not reach significance (overall relative risk 0.93; 95% confidence interval [CI] 0.83 to 1.05) but suggested that platinum agents were better than nonplatinum agents, and there was equivalence in the effect of carboplatin and cisplatin [34]. An updated Cochrane systematic review by the AOCTG, using individual patient data from 49 trials involving 863 women, compared combination nonplatinum chemotherapy versus the same combination, including platinum. They demonstrated that there was improved survival in the platinum group (hazard ratio for survival 0.88, 95% CI: 0.79–0.98). There was no significant difference between single and combination platinum-based regimens. No significant difference was observed between carboplatin and cisplatin treatment in terms of survival.

**Paclitaxel**

The taxanes are a group of drugs initially derived from the bark of the Pacific yew (Taxus brevifolia) and were first introduced into clinical practice for ovarian cancer in the 1980s. Paclitaxel was found to be active in women with relapsed ovarian cancer. It was then combined with platinum agents in clinical trials of first-line chemotherapy. The GOG 111 trial randomized women with suboptimally debulked disease to receive cisplatin and paclitaxel versus cisplatin and cyclophosphamide [35]. The results demonstrated improved overall survival for the paclitaxel arm (38 vs. 24 months; p < 0.001) and were confirmed by the OV10 study from the European/Canadian Intergroup [36].

As paclitaxel has activity as a single agent, it was then compared against paclitaxel/cisplatin and cisplatin alone in the GOG 132 study [37]. However, paclitaxel alone was not as effective as those regimens including cisplatin. The surprise finding was that there was no difference between single-agent cisplatin and paclitaxel/cisplatin (30.2 vs. 26.0 months overall survival respectively – not significant – though the study suffered a major flaw due to the number of patients eventually crossing over and receiving paclitaxel.

The largest study evaluating paclitaxel was the International Collaborative Ovarian Neoplasm Group (ICON)3 trial which compared carboplatin or cyclophosphamide/doxorubicin/cisplatin (CAP) with carboplatin/paclitaxel and recruited a total of 2074 women. The complex taxane-free control arm was an extension from the ICON2 trial, which had compared carboplatin/CAP and found them to be equivocal (although these results were unavailable when ICON3 was designed) [38]. ICON3 demonstrated no
significant difference in terms of survival between the two groups – carboplatin alone had fewer side effects than carboplatin/taxane.

The results of GOG 111, OV10, GOG 132 and ICON3 were hotly debated (for summary of results see Table 5). A meta-analysis of these four trials was complicated because of the differences in the different study arms (heterogeneity), although there was a nonsignificant trend towards superiority of combination platinum/paclitaxel (overall survival hazard ratio [HR] 0.82, 95% CI; 0.66–1.02) [39]. The study went on to statistically explore the four theories which were used to explain the different individual study results:

- Differences in crossover to taxanes in the control arm
- Differences in patients
- Differences in effectiveness of research arm regimens
- Differences in effectiveness of control arm regimens

The theory was that the two trials which demonstrated improved outcome with a combination of paclitaxel and platinum did so because the therapy in the control arm may have been suboptimal. The conclusions were ‘that single-agent carboplatin is a safe and effective first-line treatment for women with advanced ovarian cancer.’ Nevertheless, the debate continues and even the National Institute for Clinical Excellence (NICE), the government medical advisory group in the UK, recommended platinum as obligatory first-line therapy, with the use of paclitaxel, dependent on the patient/doctor. Given the intense professional disagreement on this matter, this is a difficult decision for any woman and her physician, and it must be almost impossible, without blind objectivity, not to opt for combination treatment ‘just in case.’

Since the introduction of carboplatin, there has been evidence to suggest equivalence to cisplatin, in terms of efficacy, but with less toxicity (see above). Several studies have also found this to be true when used in combination with paclitaxel [40–42], with no neurotoxicity demonstrated in women treated with carboplatin/paclitaxel, compared with 13% of women 2 years after completing treatment [40]. Carboplatin is now recognized as standard treatment.

Synthetic taxanes have been developed and one, docetaxel, has been compared with paclitaxel in The Scottish Randomized Trial in Ovarian Cancer (SCOTROC) [43]. A total of 1077 women with FIGO Stage I–IVC disease were randomized to docetaxel/carboplatin or paclitaxel/carboplatin. The two arms were equivalent in terms of survival, but with differing toxicity profiles; myelosuppression was more common with docetaxel and neuropathy was more common with paclitaxel, with docetaxel scoring better on a quality of life analysis.

**Other drugs**

Responses in women with recurrent ovarian cancer to topotecan, gemcitabine and pegylated liposomal doxorubicin have been demonstrated in Phase II and III trials [44–47]. Some of these agents are being evaluated for use in combination for first-line therapy. A large multinational trial (GOG 182 in North America and ICON5 in Europe) has closed with over 4000 women randomized to one of five arms, and will assess the efficacy of several new drugs in combination with carboplatin and paclitaxel (Table 6).

### Intraperitoneal chemotherapy

For a largely intraperitoneal tumor, such as ovarian cancer, the potential benefit of intraperitoneal therapy is that a much higher concentration of chemotherapeutic agent can be delivered to the tumor site, without increasing the systemic toxic effects, hence improving the therapeutic ratio. The GOG 114 study

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**Table 5. Randomized controlled trials of platinum versus platinum/taxane.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of women</th>
<th>Patients included (%)</th>
<th>Overall survival (months)</th>
<th>Significance</th>
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<tbody>
<tr>
<td>GOG 111</td>
<td>410</td>
<td>100%</td>
<td>–</td>
<td>38</td>
</tr>
<tr>
<td>OV10</td>
<td>680</td>
<td>63%</td>
<td>30%</td>
<td>35</td>
</tr>
<tr>
<td>GOG 132</td>
<td>424</td>
<td>100%</td>
<td>–</td>
<td>26</td>
</tr>
<tr>
<td>ICON3</td>
<td>2074</td>
<td>46%</td>
<td>34%</td>
<td>36.1</td>
</tr>
</tbody>
</table>

GOG: Gynecologic Oncology Group; ICON: International Collaborative Ovarian Neoplasm Group; NS: Not significant; OV10: European/Canadian Intergroup.
randomized women with Stage III ovarian cancer following surgery [48]. Women with tumor nodules greater than 1 cm were excluded. A total of six cycles of intravenous cisplatin/paclitaxel was compared with two cycles of intravenous carboplatin followed by six cycles of intravenous paclitaxel and intraperitoneal cisplatin. There was an improvement in progression-free survival (28 vs. 22 months; p = 0.001) and in overall survival (63 vs. 52 months; p = 0.05) although the experimental arm received more cycles of chemotherapy than the control group. A previous study had already confirmed the benefits of intraperitoneal therapy, comparing intraperitoneal cisplatin and intravenous cyclophosphamide with the intravenous therapies. Of over 654 women randomized, the median survival for intraperitoneal therapy was 49 months compared to 41 months, p = 0.02 [49]. Problems specific to the intraperitoneal group comprised gastrointestinal side effects, especially abdominal pain. However, a Phase III trial comparing intraperitoneal cisplatin with no further treatment in women with a complete response following primary surgery and chemotherapy, demonstrated no survival benefit for intraperitoneal cisplatin [50]. Problems specific to the intraperitoneal therapies are gastrointestinal side-effects, especially abdominal pain and in conjunction with the placement of intraperitoneal catheter, compared with outpatient intravenous therapy, is presumably why such treatment is not more commonly utilized. Intraperitoneal treatments continue to be assessed as part of clinical trials.

**Relapsed disease**

Unfortunately, despite a good initial response to chemotherapy, most women with advanced ovarian cancer will relapse and subsequent treatment is unlikely to result in cure. The aim at clinical relapse is therefore to relieve disease-related symptoms or delay their onset and improve quality of life, in addition to prolonging it. It is possible to predict clinical relapse in many women by monitoring serum CA125 levels, which will start to increase a median of 63 days prior to clinical progression [51]. However, whether commencing treatment at this stage is beneficial has not yet been proven, and is being addressed in an ongoing EORTC/Medical Research Council (MRC) study.

Response to chemotherapy in relapsed disease is strongly correlated with the interval between the end of their previous chemotherapy and time of relapse [52]. Women who had a treatment-free interval of less than 12 months had a response rate of 17%, whereas those with a treatment-free interval greater than 2 years had a response rate of 57%.

All of the chemotherapeutic agents currently being evaluated in the GOG 182/ICON5 trial for first-line treatment have been shown to have activity as single agents in relapsed disease (including platinum agents) (Table 6). Response rates reported are in the region of 15–30% in Phase II studies. In several Phase II trials, prior to its introduction as first-line treatment in ovarian cancer, responses to single-agent paclitaxel in recurrent disease were between 20–48% [53,54]. The ICON4/AGO study compared carboplatin with carboplatin and paclitaxel in women who had relapsed with a treatment-free interval of more than 6 months. A total of 802 women were randomized. The median survival for combination therapy was 29 months, compared with 24 months for the carboplatin-alone arm (HR = 0.82; p = 0.02) [55]. Complicating the results of this trial were facts such as, all patients had not been exposed to taxanes in first-line therapy, the sequential nature of administration in the study, and the delay and dose reduction required in some of the study arms. A smaller Phase II study seemed to support the findings of the enhanced survival with the addition of paclitaxel in the relapse setting [56].

Caelyx® (Schering Plough) is doxorubicin delivered in polyethylene glycol (PEG)-coated liposomes. Unmodified doxorubicin has been used in first-line ovarian chemotherapy, and may be responsible for the small survival advantage demonstrated in a meta-analysis when used in combination with cyclophosphamide and cisplatin [57]. However, none of the four randomized trials on their own were large enough to demonstrate an effect. In the pegylated form, doxorubicin has altered pharmacokinetics, prolonging its half-life and improving the therapeutic index. Cardiotoxicity has been a major concern with prolonged doxorubicin therapy. Pegylated liposomal doxorubicin had a less cardiotoxic effect in animal studies [58]. A Phase III trial in women with recurrent ovarian cancer comparing caelyx with topotecan demonstrated improved survival for women randomized to caelyx (median survival 63.6 vs. 57.0 weeks; HR = 1.23; 95% CI; 1.01–1.50) [46].

There are currently several agents which have proven valuable in relapsed disease. A proposed study from the GOG (GOG 213) aims to address which agents in combination give
improved survival and whether sequential or simultaneous treatment is favored. Until these results are available current treatment of relapsed disease will focus on carboplatin and paclitaxel in platinum-sensitive disease, or choosing from a range of chemotherapeutic agents for platinum-resistant disease which give similar response rates from the available, Phase II trials: caelyx [59]; gemcitabine [60]; etoposide [61]; docetaxel [62]; vinorelbine [63]; topotecan [64]; epirubicin [65] and capecitabine [66].

Novel therapies
As our understanding of the genetic basis of cancer is growing, so new targets for drug therapy are being discovered. These targets are more specific to cancer cells, so it is anticipated that potential therapeutic agents will have a specific antitumor effect, thus sparing normal cells and reducing side effects.

Tyrosine kinase inhibitors
Members of the epidermal growth factor receptor (EGFR) family are overexpressed in many epidermal-derived tumors and activation stimulates proliferation, invasion and survival of tumor cells. Once bound to its ligand, the receptor dimerizes and is phosphorylated by the intracellular tyrosine kinase domain of the receptor, triggering downstream signal cascades. Tyrosine kinases are enzymes that are central to the internal regulation of the cell. They regulate apoptosis, cell-cycle progression, immune response, differentiation and development and are often dysregulated in cancers [67].

Gefitinib is an orally active drug that blocks the EGFR tyrosine kinase, hence preventing signal transduction. It has shown promising activity in preclinical studies and a Phase I clinical trial in a range of solid tumors, including ovarian, found it to be well-tolerated [68]. The major side effects were an acne-like rash and diarrhea – stabilization of disease was demonstrated in some patients. Erlotinib is another EGFR tyrosine kinase inhibitor and has shown activity and safety in Phase I trials [69]. Both of these agents have been predominately trialed in non-small cell lung cancer, although they are likely to have an effect in any EGFR-positive tumor.

Monoclonal antibodies
Human EGFR 2 (HER2) is overexpressed in several tumors and is related to the severity of disease in breast cancer. A humanized murine monoclonal antibody (mAb), trastuzumab, has been developed that binds specifically to HER2. Its effect is dependent on an intact Fc domain, and hence may stimulate antibody dependent cellular toxicity. In a Phase II trial of 41 women with recurrent ovarian cancer, an overall response rate of 7.3% was demonstrated with no significant toxicities [70]. One of the entry criteria was HER2 overexpression and of the 837 women screened, 95 (11.4%) were identified. IMC-C225 (cetuximab) is another humanized murine mAb which binds to EGFR (HER1/ErB1) and is being evaluated in clinical trials. In preclinical studies it was capable of acting synergistically with topotecan in ovarian cancer cell lines [71].

HEA125xOKT3 is an artificial antibody which carries two different antigen-binging sites; one against the Ep-CAM antigen, which is over-expressed on epithelial tumor cells; and the T-lymphocyte antigen CD3. In preclinical studies, this antibody was able to direct tumor-associated lymphocytes to lyse tumor cells. In a Phase I clinical trial the antibody was able to produce a complete or partial reduction in ascites in all ten women, in addition to stabilizing or reducing levels of the tumor marker CA125 [72]. This treatment was well tolerated and may provide a valuable palliative treatment in ovarian cancer.

Gene therapy
Gene therapy is the use of DNA as a therapeutic agent. Cancer is essentially a genetic disorder – heritable and spontaneous mutations within individual cells lead to the development of a malignant phenotype. Many of these mutations have been discovered, such as loss or mutation of wild-type p53, and are potential targets for corrective gene therapy. Replacement of wild-type p53 for ovarian cancer gave promising results in preclinical and Phase I clinical trials [73]. However, a Phase II/III clinical trial using an adenoviral vector to deliver wild-type p53 was halted due to adverse events in the experimental arm [74]. These were due to problems associated with siting the catheter.
Executive Summary

- Epithelial ovarian cancer is the lead cause of mortality in gynecologic oncology in the developed world.
- Symptoms are vague and many women present at an advanced stage.
- Radical debulking surgery is the first-line treatment of advanced disease, although evidence for this is currently under investigation.
- First-line chemotherapy is based on carboplatin.
- There is much debate as to the additional benefit of paclitaxel in first-line chemotherapy.
- In recurrent disease, there are a variety of active agents with 15–30% response rates.
- Novel treatments include tyrosine kinase inhibitors, monoclonal antibodies and gene therapy.

for intraperitoneal delivery, in addition to adhesion formation and abdominal pain, secondary to an inflammatory reaction to the adenoviral vector.

One of the major hurdles in gene therapy is to get the therapeutic gene to the target site and to express it within the target cells. Non-viral vectors have been developed, but currently most gene therapy is delivered by viruses. Viruses have evolved to enter cells and hijack the cellular mechanisms to allow viral gene expression, often at high levels. Thus viruses can be modified to include a therapeutic gene. A prime example of this in cancer therapy is virus-directed suicide gene therapy (VDS). A virus is used to specifically express an enzyme within a cancer cell. This enzyme is then able to convert an inactive produg into a power chemotherapeutic agent. In this way, high levels of chemotherapeutic agents can be generated locally, thus improving the therapeutic effect without increasing toxicity. Various enzyme–produg combinations have been developed, for example: thymidine kinase/gancyclovir; cytosine deaminase/5-fluorocytosine; nitroreductase/CB1954 and cytochrome P-450/cyclophosphamide. Many of these have been employed in preclinical and early clinical trials. A Phase I trial of thymidine kinase and gancyclovir using an adenoviral vector in women with recurrent ovarian cancer was well tolerated and a Phase II/III trial has commenced [75].

Tumor-specificity can be achieved by targeting the virus to the tumor cell with genetic modification of the viral cellular binding domains [76], using bispecific linker molecules to bind both virus and target cell [77], or by coating the virus and binding a new receptor ligand to the coat [78]. In addition transgene expression can be limited to tumor cells by expressing the therapeutic transgene under the control of a tissue- or cancer-specific promoter such as telomerase [79,80].

Most viruses used so far in gene therapy are replication incompetent. However, adenoviral replication leads to cellular lysis and can be exploited to directly target and kill cancer cells. In wild-type adenovirus, the E1B gene product binds and inactivates p53, allowing the virus to drive the cell into an active state to enable viral replication. ONYX-015 is an adenovirus that has the E1B 55 kD gene deleted, and is only able to replicate in and lyse cells lacking wild-type p53. A Phase I clinical trial in 16 women with recurrent ovarian cancer has been completed and safety and toxicity determined. The main toxicities were flu-like symptoms, nausea and abdominal pain. However, there were no clinical responses noted, although the trial was not powered to assess response [8]. This is a problem common to most gene therapy currently that, although promising preclinically and safe in Phase I trials, efficacy in patients is limited by delivery of the vector to the target site. Therefore, whilst there are many therapies which have great potential, the barrier of efficient delivery of genetic material remains to be overcome.

Expert opinion & outlook

Most women with ovarian cancer present at a late stage and continue to die from their disease although improvements in treatment are slowly improving survival, which is turning treatment of ovarian cancer into a form of chronic disease management. There is a growing recognition for the need to enroll women into clinical trials, to test both new treatment options and long-held beliefs, and it is to be hoped that this will increase the speed of improvements in clinical outcome. Increasing understanding of the molecular mechanisms that underlie the development of cancer are providing new targets for therapy and novel means to provide treatment, which hope to improve survival and quality of life, by limiting side effects. However, much work is needed to translate advances in the laboratory into improvements for patients. This will require increasing collaboration between clinicians, scientists and patients. It is likely that novel therapies will need to be targeted to patients and the next 10 years are likely to see a move from the ‘one-size-fits-all’ approach of chemotherapy, to a more patient-oriented approach, based both on the woman’s preferences as well as her tumor phenotype/genotype.
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