Optimal treatment for relapsing ovarian cancer

J. A. Ledermann* & R. S. Kristeleit
UCL Cancer Institute, University College London, London, UK

The cure rate for women with ovarian cancer has not significantly changed over the past 10 years. However, overall survival from relapsed disease has shown improvement despite a lack of increase in progression-free survival. There are now many therapeutic options for women with relapsed disease. Treatment strategies are still led by the description of relapse as platinum sensitive or resistant/refractory using somewhat arbitrary definitions. Now that there is increased choice of treatment, these definitions are becoming outdated. The current challenges in managing relapsed ovarian cancer are defining the optimal sequence of available drugs as well as timing of treatment for relapsed disease. The abundance of novel therapeutics and molecular targets has compounded the difficulty in identifying best practice but has undoubtedly provided an opportunity to improve the treatment we can offer our patients. The lack of validated biomarkers to inform patient selection remains an area of real need in ovarian cancer. Efforts should be made to increase the use of biomarkers in trial design to aid rational targeting of new therapies. In this review we discuss current practice in the treatment of relapsed ovarian cancer and highlight the most promising emerging therapeutics and strategies being employed in randomized clinical trials.

*Correspondence to: Prof. J. A. Ledermann, CRUK and UCL Cancer Trials Centre, 90 Tottenham Court Road, London W1T 4TJ, UK. Tel: +44-20-7679-9898; Fax: +44-20-7679-9899; E-mail: j.ledermann@ctc.ucl.ac.uk

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introduction

Over the past decade there has been little improvement in the cure rate of ovarian cancer. During this time the combination of carboplatin and paclitaxel has remained as the standard first-line therapy. Response rates to this combination are in the region of 70%–80%, but the majority of these women subsequently relapse and are then deemed incurable. Progression free survival (PFS) after first-line therapy has not increased but overall survival (OS) is now longer [1]. This may be due to better use and choice of drugs as well as improved patient care.

Many patients now receive several lines of treatment following recurrence as the number of available therapies has increased. However, decisions about the most appropriate treatment and the timing of therapy at relapse are complex. During the past decade the results of clinical trials have been increasingly important in guiding these decisions. We have now entered a new era where molecular agents directed at several different targets known to be involved in ovarian cancer present new opportunities for treatment. These novel drugs are being investigated in clinical trials as single agents or in combination with chemotherapy.

Decision-making is based primarily on whether patients are categorized as having ‘platinum-sensitive’ or ‘platinum-resistant’ disease. These definitions are >20 years old and were based on practice at a time when there were few alternatives to retreatment with cisplatin. Resistance to platinum is a continuous time variable and although these definitions remain important in guiding treatment, other considerations in an individual patient, such as the distribution of disease, toxicity profile and patient preference (e.g. hair loss) need to be taken into account. It is now time to reconsider how to classify the probability of response to retreatment, as there is a greater choice of drugs and opportunities for different schedules, such as dose-dense platinum or non-platinum-containing regimens in platinum-sensitive disease. The search for biomarkers that predict response, and particularly a molecular marker to define patients with ‘platinum-sensitive’ tumours remains an elusive goal.

Here we review some of the current challenges to decision-making in the management of relapsed ovarian cancer, focusing on the results of recent and ongoing clinical trials with cytotoxic drugs and novel molecular targeted agents (Table 1).
Table 1. Ongoing randomized trials with molecular targeted agents in relapsed ovarian cancer

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Chemotherapy</th>
<th>Phase</th>
<th>Trial number</th>
<th>Placebo n</th>
<th>End point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum-sensitive relapse</td>
<td>VEGF</td>
<td>Bevacizumab</td>
<td>Platinum–taxane</td>
<td>III NCT00566851 (GOG 213)</td>
<td>N 660 OS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VEGF</td>
<td>Bevacizumab</td>
<td>Platinum–gemcitabine</td>
<td>III NCT00434642 (OCEANS)</td>
<td>Y 450 PFS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VEGFR1, 2, 3</td>
<td>Cediranib</td>
<td>Platinum-based</td>
<td>III NCT00532194 (ICON 6)</td>
<td>Y 2000 OS</td>
<td></td>
</tr>
<tr>
<td>Folate receptor-α</td>
<td>Folatuzumab</td>
<td>Platinum–taxane</td>
<td>III NCT00849667</td>
<td>Y 900 PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARP</td>
<td>Olaparib</td>
<td>Platinum-based</td>
<td>II NCT00753545 (Study 19)</td>
<td>Y 250 PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Src kinase</td>
<td>AZD0530</td>
<td>Platinum–taxane</td>
<td>II NCT00610714 (OVERT 1)</td>
<td>Y 241 RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelin A</td>
<td>Zibotentan</td>
<td>Platinum–taxane</td>
<td>II NCT00929162</td>
<td>Y 122 PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum-resistant relapse</td>
<td>Bevacizumab</td>
<td>Paclitaxel, Topotecan, Liposomal doxorubicin</td>
<td>III NCT00976911 (AURELIA)</td>
<td>N 300 PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARP</td>
<td>Olaparib</td>
<td>Liposomal doxorubicin</td>
<td>II NCT00628251 (ICEBERG3)</td>
<td>N 90 PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGFR2, 3/PDGFR-β/c-Kit</td>
<td>Sorafenib</td>
<td>Topotecan</td>
<td>II NCT01047891 (TRIAS 2009)</td>
<td>Y 184 PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folate receptor-α</td>
<td>Farlatuzumab</td>
<td>Paclitaxel</td>
<td>II NCT00738699</td>
<td>Y 350 PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGFR2/EGFR</td>
<td>Vandetanib</td>
<td>Docetaxel</td>
<td>II NCT00872989</td>
<td>N 120 PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-1R</td>
<td>OSI-906</td>
<td>Paclitaxel</td>
<td>II NCT00889382</td>
<td>Y 199 GCIG Ca125 RR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

 EGFR, epidermal growth factor receptor; IGF, insulin-like growth factor; PARP, poly(ADP-ribose) polymerase; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; OS, overall survival; VEGF, vascular endothelial growth factor

several hours so that in most cases cisplatin is substituted. In the majority cross-hypersensitivity is not a problem but it does occur in some patients, usually after several further cycles.

combination therapy
The ICON4/OVAR 2.2 trial was the first large-scale randomized phase III trial to compare the addition of a second drug to platinum-based therapy. Paclitaxel added to platinum, usually carboplatin, extended both the PFS and OS of patients with recurrent ovarian cancer. More than 90% were treated in first relapse and ~75% received treatment after a platinum-free interval of >12 months. PFS at 1 year was increased significantly with an increase in the median PFS of 3 months (13 compared with 10 months). The small benefit in survival, corresponding to an absolute difference of 7% at 2 years (57% compared with 50%) has to be balanced against the morbidity of further hair loss and possible peripheral neuropathy [3]. A similar magnitude of improvement in PFS was seen in the AGO-OVAR-led intergroup trial when gemcitabine was added to carboplatin, although there was no increase in OS [4]. The combination of carboplatin and gemcitabine is well tolerated by patients but does cause significant myelosuppression, often resulting in treatment delays. Both combination regimens are commonly used in practice. A recent randomized phase III non-inferiority trial has compared carboplatin–liposomal doxorubicin (PLD) with carboplatin–paclitaxel. This has shown lower toxicity for the combination with PLD and the PFS was as good as, or slightly better than, carboplatin–paclitaxel [5]. Patients on the carboplatin–PLD arm were treated for longer; interestingly the incidence of carboplatin hypersensitivity in this arm was much lower. The OS results are awaited. Even if no differences in OS emerge it is possible that this combination, because of its lower toxicity may become a regimen of choice in the platinum-sensitive population. The choice of therapy in patients with platinum-sensitive relapse has recently become more complicated following the results of a randomized trial comparing PLD with PLD and the DNA minor-groove binder, trabectedin (OVA-301) [6]. This combination leads to improved PFS and OS, and the effect is particularly striking in patients with tumours that are 'partially platinum-sensitive', i.e. relapsing within 6–12 months of a previous line of platinum [7]. This is the first study to show a survival benefit using non-platinum drugs. It provides an opportunity of delaying further platinum therapy. Thus, PLD, which was formerly mainly used in platinum-resistant tumours, now has a more prominent place in the treatment of 'platinum-sensitive' disease. The choice of partner drug is unclear but a trial to compare carboplatin–PLD with PLD–trabectedin is being planned.

timing of relapse treatment
Most patients are followed by routine clinical assessment and measurement of CA125. Relapse may be defined using Gynecologic Cancer Intergroup (GCIG) criteria, and this often occurs several months (median 3 months) before clinical or radiological relapse. This has led to uncertainty about the appropriate timing of reintroducing chemotherapy. In some cases retreatment is made on the basis of CA125 alone as it is thought that early treatment will lead to an improvement in outcome. In other cases decisions are based more on clinical symptoms or radiological changes. Recently a trial conducted by the NCRI and EORTC OV05/EORTC55955 compared retreatment based on a doubling of CA125 above the upper limit of normal with treatment determined by conventional clinical assessment. Patients were entered into the study after completion of first-line therapy and normalization of CA125. In those relapsing, treatment was started a median of 4.8 months earlier but Rustin et al. [8] clearly showed that survival was unaffected by the early institution of chemotherapy. Furthermore, third-line treatment was also started a median of...
4.6 months earlier. These results may have implications for the follow-up of patients with ovarian cancer.

**surgery**

The role of surgery for recurrent disease remains unclear. There is currently evidence from randomized trials to support second surgery in ovarian cancer. For those that believe surgery has a role the results are likely to be best when it is performed in patients who previously had no residual disease after primary surgery, small volume disease, absence of ascites and have 'platinum-sensitive' relapse [9]. The possibility of second surgery is perhaps the strongest argument for continuing to measure CA125 after first-line therapy. The prognostic determinants of a favourable outcome (DESKTOP I) have recently been validated in a multinational study, DESKTOP II and a randomized trial has recently started (DESKTOP III). In the USA the GOG#213 trial with carboplatin–paclitaxel with or without bevacizumab also has a randomization to second surgery.

**treatment of platinum-resistant and refractory ovarian cancer**

Ovarian cancer relapsing within 6 months of platinum treatment represents a heterogeneous spectrum of disease with a low response rate to therapy (~10%–25%), generally of short duration. Attempts to identify patients who will respond to specific drugs are challenging [10]. True platinum-resistant, or refractory disease is more readily defined than 'platinum-resistant' ovarian cancer. In general most clinicians use non-platinum drugs in both groups. However, recent evidence from non-randomized trials suggests dose-fractionated weekly therapy may partially overcome platinum resistance. High response rates have been reported with carboplatin and weekly paclitaxel [11, 12]. The main goal of treatment in this group of patients is maintaining quality of life by preventing and controlling symptoms so the selection of drugs and schedule of treatment should always take account of these aims. The benefit of the chemotherapy treatments with modest response rates used in this setting compared with best supportive care has not been evaluated in clinical trial.

**chemotherapy**

Whilst there are many drugs that have been studied in 'platinum-resistant' disease the lack of data from randomized trials means there is limited evidence-based guidance for a particular regimen [13]. Most randomized studies include patients with some degree of platinum sensitivity. Even in 'positive' trials subset analyses fail to show differences between drugs in the platinum-resistant population [14]. A general recommendation can be made for the use of monotherapy with liposomal doxorubicin, topotecan, etoposide, gemcitabine or paclitaxel. For the latter, there is increasing evidence that its activity is improved using a weekly schedule [15]. In the absence of biomarkers predictive of response or convincing data demonstrating efficacy of one agent over another, there is no current preferred sequence of agent or means to select a sensitive population. Clinical judgment, therefore, continues to play an important role in management.

**endocrine therapy**

Endocrine therapy has not been evaluated systematically in relapsed resistant ovarian cancer but is widely used [16]. Small randomized studies in heavily pretreated patients have failed to show an advantage of hormone therapy, such as leuprorelin or tamoxifen, over chemotherapy, but as the benefit of either approach is small the use of well-tolerated hormone therapy may be a reasonable choice in selected patients [17, 18].

**emerging compounds and molecular targets**

Pemetrexed, a multitargeted antifolate agent inhibiting thymidylate synthase has encouraging activity in early relapsed disease [19] with recent evidence describing response rate in platinum-refractory or -resistant ovarian cancer similar to other currently used agents [20]. The activity of epothilones, novel microtubule inhibitors, is also being explored. These drugs are active in ovarian cancer [21] but there is no evidence to suggest that their use in platinum-resistant disease might be more favourable than other chemotherapeutic agents [22]. A randomized phase III study comparing patupilone with liposomal doxorubicin in ‘platinum-resistant’ and ‘refractory’ disease is currently ongoing (clinicaltrials.gov, NCT00262990).

Angiogenesis has a major role in ovarian cancer and circulating vascular endothelial growth factor (VEGF) levels are often raised in ovarian cancer. Antiangiogenic agents, including many small molecule VEGFR tyrosine kinase inhibitors (TKIs) (e.g. cediranib, sorafenib) as well as antibodies (e.g. bevacizumab, VEGF trap), have been the most extensively investigated targeted therapies in ovarian cancer [23]. Tumour response rates to single-agent bevacizumab in heavily pretreated patients with ovarian cancer are similar to those seen with chemotherapy. It also appears that bevacizumab delays tumour progression [24, 25]. There are concerns about a high rate of intestinal perforation seen in some studies, and patients need to be carefully selected. The results of the OCEANS study, a randomized trial in which bevacizumab is added to carboplatin and gemcitabine are awaited with interest.

The molecular targets commonly implicated in drug resistance in ovarian cancer are multiple nodes within the PI3K/AKT/mToR pathway [26, 27], insulin-like growth factor receptor (IGFR) [28, 29] and src kinase [30]. There are now several agents that inhibit these targets (Fig. 1) and early phase clinical studies are ongoing to evaluate toxicity and the optimal dose of these drugs. The classical principles of dose–response and toxicity applied to phase I investigations of cytotoxic agents are not directly transferable to biological therapies. In the absence of biomarker end points, these agents need to be assessed in randomized trials at an early stage of their development. One approach used in a study with BIBF 1120, a triple angiokinase inhibitor, has been to conduct a randomized placebo-controlled phase II trial in patients following the completion of relapse chemotherapy. Prolongation of the progression-free interval at a fixed (9-month) time point has
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Figure. 1. Novel agents in phase I/II development targeting pathways associated with chemoresistant ovarian cancer

indicated that vargatraf has worthwhile activity and a large-scale study in first-line therapy is now underway [31].

Drugs targeting the folate receptor-alpha (FR-α) such as farletuzumab [32] and BGC945 [33] are a further important experimental class of agents that are being explored in ovarian cancer. As the FR-α is commonly overexpressed in ovarian cancers but rarely in normal tissues these drugs have the potential to be truly tumour-targeted therapy [34]. Farletuzumab is currently being evaluated in phase II and III trials in relapsed ovarian cancer, which includes a platinum-resistant population, whilst BGC945 has just entered phase I testing.

The greatest success in identifying a tumour target for therapy has resulted from studies with inhibitors of the DNA repair enzyme, poly(ADP)ribose polymerase (PARP). Patients with germline mutations of BRCA 1 or 2 have impaired mechanisms to repair DNA damage. In these patients their tumours are more sensitive to PARP inhibitors (PARPi) as they compound the defective repair of DNA damage [35]. Several PARPi are now in clinical trials. Tumour responses have been seen with single-agent therapy [36, 37]. Randomized trials are being performed, comparing PARPi with chemotherapy. The results of the first of these studies comparing olaparib (AZD2281) will soon be available. Defective DNA repair may also occur in high-grade serous tumours without inherited mutations of the BRCA genes [38, 39]. Some of these tumours have a 'BRCAness' phenotype and may also be susceptible to PARPi [40]. A randomized trial (study 19) comparing PFS following olaparib or placebo in patients with high-risk serous tumours completing chemotherapy for relapsed disease has just been completed (see Table 1). The results will be available in 2011. It is now emerging that the efficacy of PARPi as a single agent is greater in 'platinum-sensitive' tumours and it is probably this group of patients who are likely to derive greatest benefit from this class of drug [41].

conclusions

Therapeutic possibilities in relapsed ovarian cancer have increased significantly over the past 5 years. Simple concepts of choosing between single or combination therapies have been replaced by complex decision-making, selecting the best sequence of drugs for patients. This has been further complicated by the explosion in molecular targeted agents that are now available for study. Several of these are now in trials. Many of these trials have been set up using carboplatin–paclitaxel as the standard arm and some of these studies may need to be repeated if carboplatin–PLD becomes a new standard of care. One might argue that if the main role of antiangiogenic agents is to prolong remission they may best be used in patients with recurrent disease, as the primary aim of first-line therapy is to increase the cure rate. It is becoming clear from studies in a variety of cancers that prolonged therapy with antiangiogenic agents is needed to extend remission, or control of the disease. This has major economic implications as well as effects on patients’ quality of life. Interpretation of the results will be challenging, particularly if positive results emerge from several different classes of compound. It is clear that unless we identify specific molecular targets within patients we will continue to make relatively arbitrary choices about which therapies to use to manage recurrent ovarian cancer. If real progress in therapy is to occur it is vital that research into the pathobiology of ovarian cancer continues in parallel, and in connection with randomized clinical trials.

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