Clinical trials and decision-making strategies for optimal treatment of relapsed ovarian cancer

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Abstract

The proportion of patients with advanced ovarian cancer who relapse has remained high and fairly constant over the last decade. Choosing treatment for recurrent ovarian cancer is complex. Many active therapeutic agents are available, and there are challenges in defining the optimal timing and sequencing of treatments. Furthermore, the explosion in the number of biological agents presents additional challenges in identifying their activity and place in the pathway of treatment. Establishing optimal treatment as monotherapy, or in combination with chemotherapy, or as maintenance treatment requires new approaches to trial design, selecting meaningful endpoints and conducting carefully conducted trials with translational studies. Patients with relapsed ovarian cancer can now survive several years; the aim is to increase this further.

Introduction

The survival of patients with ovarian cancer has increased over the last 20 years because of improvements in clinical management and the introduction of new therapies. In 2006, a trial in advanced ovarian cancer reported a median survival of over five years for the first time [1]; however, the median time to relapse in most studies remains remarkably constant at about 18 months. In the modern era of ovarian cancer treatment, the period of managing disease recurrence is often considerably longer than the phase of first-line therapy to relapse. In some patients ovarian cancer behaves like a 'chronic disease' with some patients surviving many years. Patients commonly undergo multiple lines of treatment to extend survival and control symptoms. However, the time interval between consecutive courses of treatment becomes progressively shorter or disappears until treatment is no longer possible either due to acquired resistance to all available drugs, or patient exhaustion. These features raise important issues for clinicians and patients around understanding and defining triggers for treatment initiation, and restraint to prevent over-treatment, particularly in the earlier phase of recurrence. As cure is rarely possible after recurrence, maintenance or improvement in quality of life and prolongation of survival are the key objectives.

One of the most frequently used definitions to predict response in recurrent ovarian cancer is 'platinum-sensitivity'. This term is best regarded as a continuum, with an increasing probability of chemo-sensitivity to re-challenge with platinum drugs over the time from initial treatment to recurrence. Disease that recurs more than two years after initial therapy has a response rate approaching that of first-line treatment [2]. Over time the definition of 'platinum-sensitivity' has been amended without detailed further study to include third- and subsequent line therapy, and the selection of platinum combination therapies. For the purpose of guiding the choice of therapy, the time to relapse is divided into six-month blocks. Patients who relapse during or immediately following platinum-based chemotherapy are defined as having 'platinum-refractory' disease. The other disease terms are: 'platinum-resistant' for tumour relapsing under six months after last platinum therapy; 'partially platinum-sensitive', for relapse occurring with an interval of 6–12 months; 'platinum-sensitive' for disease recurring more than 12 months after platinum therapy. There are now many active non-platinum drugs to consider for treatment of recurrent ovarian cancer and there is a need to develop more relevant definitions. For example, the term 'treatment-free interval' rather than 'platinum-free' interval is used to take into account the non-platinum therapies.

Serous epithelial ovarian cancer is the most common histological subtype. However, a significant minority of patients have other subtypes such as clear cell or mucinous cancers, and these have a much worse prognosis [3]. Currently, all histological subtypes are treated in the same manner but

trials are now being developed to explore different treatments for these histological subtypes. As these tumour subtypes are uncommon, international collaborative trials are required. Examples include mEOC/GOG 241 (NCT01081262) for mucinous cancers and NCT01196429 and NCT00979992 for clear cell cancers.

Designing clinical trials

There are over 170 open clinical trials in recurrent ovarian cancer registered on the National Institute of Health trials website (http://clinicaltrials.gov/). Clinical trials address important questions about the optimal use of chemotherapy drug combinations, dose fractionation and schedules, integration of surgery and the testing of new targeted drugs. However, integrating the knowledge from these numerous studies into an improvement in clinical practice presents a significant challenge.

Phase II studies

Phase II clinical trials have been the traditional method of evaluating the activity of new drugs or treatment schedules. However, there have been concerns about the number of phase II trials that have resulted in negative phase III trials and as a consequence the wastage of resources, time and personal expense to patients. Historically, phase II trials were single-arm studies assessing tumour regression as an end-point and comparing results with historical controls [4]. However, this method of conducting trials has been criticised in the current era where there are hundreds of investigational anti-cancer therapies and where rapid changes in the standard of care weaken the fundamental assumption that historical controls are adequate comparators [5]. In addition, classical trial end-points, such as RECIST response, can be misleading in phase II trials, as they may not be the correct measure of activity for novel targeted drugs.

Randomised phase II studies that compare an experimental therapy with a current standard or with another type of experimental therapy are now commonly performed. Randomisation reduces bias in treatment selection and toxicity evaluation. Survival endpoints, such as a fixed early time point for progression-free survival is now commonly used to reduce the number of patients needed for a study. Furthermore it is possible to design a phase II/III trial where following an interim assessment the study can continue and be integrated into a large-scale phase III trial in which survival is the main endpoint. Using such designs, studies that are unlikely to lead to a significant benefit can be stopped early.

Phase III studies

Despite the large number of trials being conducted, the rate of approval for new agents has slowed (FDA, 2004). This has led to calls for a more efficient and speedy method of evaluating new agents and designing trials. Parmar and colleagues have proposed a multi-arm, multi-stage trial design that investigates the efficacy of a number of new drugs/combinations simultaneously by comparing them with a single standard control treatment arm in a randomised fashion [6]. After a planned interim analysis agents failing to demonstrate sufficient activity are rejected. The trial continues to recruit in the other arms resulting in a more efficient use of resources and patient data, and it provides a seamless progression through the stages of the trial, avoiding the multiple regulatory steps needed for separate studies. One of the first examples of this was GOG182/ICON5, a five-arm trial in ovarian cancer. However, arms were not dropped as recruitment was faster than expected and the trial completed recruitment shortly after the planned interim analysis [7]. More often, trials with novel therapies are first studied in patients with recurrent disease. The ICON6 is a three-arm study that uses a similar multi-stage design. In this trial, cediranib, a novel therapy targeting the vascular endothelial growth factor receptor (VEGFR) is combined with platinum-based chemotherapy in platinum-sensitive relapsed ovarian cancer. A key aspect of this trial is the use of the novel targeted agent in combination with chemotherapy. The trial has three stages: the first to evaluate the toxicity of the combination; the second to determine whether the addition of cediranib produces an improvement in progression-free survival, and the third part in which a large number of patients will be recruited to measure differences in survival when cediranib is added to chemotherapy, and continued beyond chemotherapy.

Conducting large, complex phase III trials such as those described above are a great challenge and require international collaboration to recruit sufficient numbers of patients in a timely fashion. The cost of conducting trials has risen steeply in Europe after stringent laws were introduced into countries following the European Clinical Trials Directive. In cases where multiple agents are trialled it is important that pharmaceutical companies collaborate with academic groups. Organisations such as the Gynecologic Cancer Intergroup and European Network for Gynaecological Cancer Trials help to bring national groups together

and partner with industry, making the conduct of trials more relevant and efficient.

One of the criticisms of the current trial design is the lack of comprehensive translational research preceding large phase III trials. Many trials include the collection of tissue samples in parallel to the running of the trials, but analyse the tissue or blood samples retrospectively. This is considered to be an illogical approach by some, as knowledge of the tumour biology is not being used to select patients likely to benefit. However, the rate of development of new agents is rapid and in many cases the tumour biology is not well understood. Understanding tumour biology is a key goal for the selection of novel agents for therapy. This applies no less to the treatment of recurrent disease when the acquisition of tumour samples at relapse presents an even greater challenge.

Decision-making strategies and timing of treatment:

Approximately 75% of patients with advanced ovarian cancer will relapse and surveillance for ovarian cancer after completion of first-line therapy varies from centre to centre. The European Society of Medical Oncology has recommended clinical history, physical examination including pelvic examination every three months for two years, every four months during the third year and every six months thereafter [8]. A CT scan is only recommended if there are clinical signs of progression or the serum CA125 is elevated. A rise in serum CA125 predicts recurrence of disease and in the majority this occurs before signs of clinical relapse [9]. However, the value of CA125-based follow-up is controversial, as the institution of second-line therapy on the basis of a CA125-defined relapse has not been found to be beneficial in terms of survival. Furthermore, knowledge of a raised CA125 and withholding treatment can cause considerable anxiety to patients. This was clearly shown in the MRC OV05/EORTC 55955 trial [10], which recruited 529 patients in complete clinical remission and with a normal level of CA125. Measurement of CA125 on follow up was blinded and patients in relapse were randomised to one of two arms: the immediate treatment arm when the CA125 level was elevated, or a delayed treatment arm when a patient developed clinical symptoms of progression. Patients in the immediate arm commenced second-line therapy a median of 4.8 months earlier than the patients in the delayed treatment arm. There was no difference in overall survival between the two arms (Hazard Ratio = 1.00; 95% CI 0.82–1.22; $P = 0.98$). In addition, quality of life was superior in the delayed treatment arm.

However, many clinicians still routinely advocate CA125 follow-up and early knowledge of a rising CA125 may be important if secondary debulking surgery is shown to have an effect on survival.

The role of the multi-disciplinary team in the management of ovarian cancer patients is crucial and has been shown to improve overall survival of patients [11]. The involvement of a number of interested and experienced clinicians' expertise in different specialties providing care in a cohesive, holistic and prompt manner is probably an important factor. However, the extent to which this impacts on the survival time following relapse is unclear and requires further study. The multi-disciplinary team should remain at the core of patient care, particularly when treatment decisions become difficult and quality of life needs to be balanced with the potential toxicities of further chemotherapy. It is generally accepted that patients who respond to chemotherapy have an improvement in quality of life scores while those who have progressive disease have a worsened quality of life [12]. Accurate prediction of response to treatment is therefore vital in preserving/enhancing quality of life and preventing unnecessary side effects, inconvenience and cost of chemotherapy in the recurrent ovarian cancer setting. Factors predicting response include, long treatment-free interval [2,13], tumour size (<5 cm), number of sites of disease and histology [14].

In platinum-resistant patients, objective response to chemotherapy is known to be poor. However, the clinical benefit achieved may still be significant from a patient's perspective. Assessing the benefit of chemotherapy treatments in this population requires an integration of traditional measures of response, e.g. radiological, CA 125 criteria and measurement of clinical benefit.

Surgery

The role of surgery in recurrent ovarian cancer is not well defined and historically its practice has varied widely from institution to institution. Current published data, albeit from non-randomised studies, supports surgical cytoreduction at relapse in carefully selected patients. Although usually not curative there may be a survival advantage. In a multivariate analysis (DESKTOP I), potential prognostic factors were found to be: long disease-free interval, single site of recurrence and no residual disease after primary surgery [15]. From the study a scoring system was

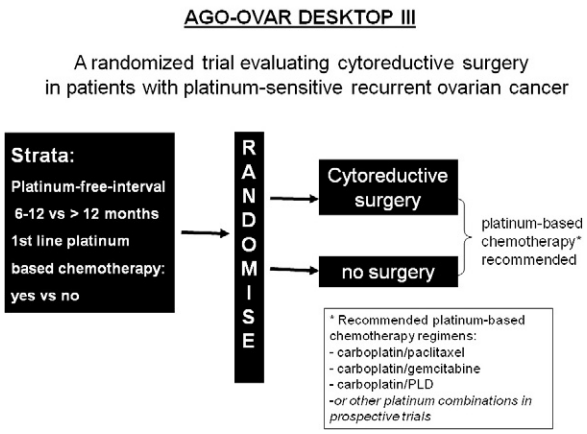

Fig. 1. AGO-OVAR DESKTOP III. A randomised trial evaluating cytoreductive surgery in patients with platinum-sensitive recurrent ovarian cancer.

proposed for the prediction of complete cytoreduction consisting of: good performance status, complete resection at first surgery (or early FIGO stage) and the absence of ascites [16]. This predictive score was successfully validated in a subsequent multicentre DESKTOP II study [17], and is now being used to select patients for a randomised prospective DESKTOP III trial (NCT00006356), which is investigating surgery in recurrent ovarian cancer (Fig. 1). A similar question about secondary surgery is being addressed in the GOG 213 (NCT00565851) study. This is a bifactorial randomised trial in platinum-sensitive ovarian cancer of carboplatin–paclitaxel with or without bevacizumab in the presence or absence of secondary surgical cytoreduction. The results of these studies will determine whether surgery has a role to play in the treatment of recurrent ovarian cancer.

Surgery can also be performed for palliation of symptoms, mainly intestinal obstruction. It should only be considered in patients who fail medical management for bowel obstruction, are fit enough to undergo surgery, and in those with localised obstruction that is technically resectable or amenable to by-pass surgery. However, objective assessments of the predictable success of surgery in terms of clinical benefit are not easy to define and this is an area that needs further research.

Radiotherapy

Radiotherapy is principally restricted to the palliation of symptoms in recurrent ovarian cancer. Symptoms of bleeding and pain, due for example to lymphadenopathy, can be treated with excellent results and relatively little toxicity [18].

Chemotherapy choices

'Platinum-sensitive' relapse – single and combination therapies

Patients relapsing >six months after completion of first-line chemotherapy are considered to have 'platinum-sensitive' disease and there is a high probability that they will respond to further platinum-based treatment. Most will be re-treated with either single-agent platinum (usually carboplatin) or platinum combination therapy. Carboplatin is usually given in preference to cisplatin unless the patient develops an allergy to carboplatin. This is not infrequent, occurring in about 20% patients who are re-challenged with the drug at relapse. Some clinicians will substitute with cisplatin without problems, whilst others will persist with carboplatin using a 'desensitisation' regimen [19].

Whilst single-agent platinum may be the treatment of choice because of co-existing morbidities or patient choice, there is now considerable evidence from randomised trials that combination therapy is superior to single-agent treatment (see Table 1).

The ICON4/OVAR 2.2 study investigated the combination of platinum plus paclitaxel compared with platinum alone in 802 patients relapsing after platinum-based chemotherapy [20]. The platinum-free interval was >12 months in ~75% of patients and 92% of patients were randomised after the first relapse. The hazard ratio for progression-free survival was 0.76 ($P = 0.0004$) and for overall survival 0.82 ($P = 0.02$) in favour of the paclitaxel–platinum regimen. The absolute difference in survival at two years was 7% (57% vs. 50%) between the paclitaxel and conventional treatment groups, and the difference in median survival was five months (29 vs. 24 months). This trial demonstrated for the first time that platinum in combination with paclitaxel significantly improved progression-free and overall survival. However, the survival benefit needs to be balanced against potential neurotoxicity and alopecia. This has underlined the need to investigate other combinations.

AGO-OVAR 2.5 with NCIC-CTG and EORTC conducted a study of the nucleoside analogue, gemcitabine in combination with carboplatin [21]. Three hundred and sixty-five patients with platinum-sensitive relapsed ovarian cancer were randomised to gemcitabine plus carboplatin or carboplatin alone. The gemcitabine arm consisted of carboplatin plus gemcitabine on day 1 and gemcitabine alone on day 8 of a three-week cycle. A significant improvement was seen in progression-free survival, the primary end-point of the trial. The median progression-free survival was

Table 1
Pivotal phase III trials in platinum-sensitive ovarian cancer

Study	Chemotherapy		No. of patients	Response rate (%)	Progression-free survival (mo)	Overall survival (mo)
	Experimental arm	Control arm				
ICON4 [20] AGO-OVAR2.2 (Parmar et al.)	Platinum plus paclitaxel	Platinum combination	802	66 vs. 54	12 vs. 9*	29 vs. 24*
AGO OVAR [21] (Pfisterer et al.)	Gemcitabine plus carboplatin	Carboplatin	356	47 vs. 31*	8.6 vs. 5.8*	18 vs. 17.3
CALYPSO [22] (Pujade-Lauraine et al.)	PLD plus carboplatin	Paclitaxel plus carboplatin	976	NA	11.3 vs. 9.4*	Not mature
OVA-301 [23] (Monk et al.)	Trabectedin plus PLD	PLD	672[a]	35 vs. 22.6	9.2 vs. 7.5*	NA

*Statistically significant.
[a] Inclusive of platinum-resistant patients.

8.6 months for the combination arm and 5.8 months for those receiving monotherapy. Overall survival was not significantly improved; however, the study was not powered to detect an improvement in overall survival. The combination was well tolerated, although there were significantly more treatment delays due to myelosuppression and the added inconvenience of further infusion of gemcitabine on day 8.

The Gynecologic Cancer Intergroup conducted the 'CALYPSO' study, a large multicentre phase III non-inferiority trial comparing standard three-weekly carboplatin plus paclitaxel with monthly pegylated liposomal doxorubicin (PLD) plus carboplatin [22]. The trial demonstrated non-inferiority of the experimental arm in terms of progression-free survival (median PFS 11.3 vs. 9.4 months; HR 0.821; 95% CI 0.72–0.94, $P = 0.05$) and a better toxicity profile. The experimental arm also had significantly less myelosuppression, hair loss, peripheral neuropathy, discontinuation of treatment and interestingly fewer carboplatin hypersensitivity reactions.

The results of this trial have led to widespread use of the carboplatin-liposomal doxorubicin regimen in platinum-sensitive relapse. Its favourable toxicity profile may lead to it becoming the most frequently used combination regimen for relapse in the future. At present, all three regimens are commonly used in clinical practice.

Recently there has been interest in using a non-platinum combination in relapsed ovarian cancer. In a randomised controlled trial PLD was given alone or in combination with trabectedin, a DNA minor groove binder. The study of 672 patients comprised a heterogeneous population of patients with relapsed ovarian cancer [23]. In a *post hoc* subgroup analysis of women with 'partially platinum-sensitive' recurrence there was a 41% reduction in the risk of death in favour of trabectedin and PLD (HR = 0.59; 95% CI, 0.43–0.82; $P = 0.0015$) In the combination arm the median survival was 23.0 compared with 17.1 months [24]. This intriguing result suggests that in this subgroup non-platinum combination therapy may be a feasible alternative to platinum, and that delaying the re-introduction of platinum may have a beneficial effect on survival. This will need to be demonstrated in a prospective randomised trial in which patients progressing after trabectedin and PLD are given platinum, and this study is now underway.

'Platinum-resistant' relapse

This group of patients comprises a heterogeneous population consisting of those who have disease progression during platinum-based chemotherapy, i.e. 'platinum-refractory' or those whose disease recurs within six months of completing treatment i.e. 'platinum-resistant' disease. It also includes those patients who have been heavily pre-treated and have acquired platinum resistance. In practice, the majority of patients with recurrent ovarian cancer will eventually develop 'platinum-resistant' disease. It is important to recognise that this is not one group of patients. Clinical trials often fail to distinguish these populations, in whom disease biology can be quite different. However, in general women in this group have tumours with a low probability of response to further chemotherapy, and a short survival. Response rates are at best in the order of 10–15%, frequently lower and the duration of response is short. Clinical trials with new agents continue to evaluate response and survival as endpoints. While the latter has some value, the former rarely provides clinically

useful information. Other parameters of palliation need to be considered, such as Quality of Life and 'Patient Reported Outcomes'. An international trial to measure this is currently in progress, led by the Australia and New Zealand Gynaecological Oncology Group, using tools that they have established to assess patient benefit. In choosing chemotherapy for this group, and there are a number of 'standard' drugs used (e.g. PLD, paclitaxel, topotecan, etoposide and gemcitabine) one needs to balance the likely effect, the toxicity profile with the underlying clinical performance status and patient preferences. In patients with a poor performance status 'best supportive care' may be the most appropriate treatment. Conversely, trials of experimental therapies could be considered in patients with a good performance status and a high level of motivation. PLD is often selected as the non-platinum option [25,26]. Other single-agent treatments include topotecan [27], gemcitabine [28], paclitaxel [29] and oral etoposide [30]. Newer agents continue to be tested in platinum-resistant ovarian cancer with some modest improvements seen with the multi-targeted anti-folate agent, pemetrexed [31] and the novel glutathione analogue, canfosfamide in combination with PLD [32]. In many cases pharmaceutical studies use PLD as the comparator, and new agents are given with PLD. There is often no clear rationale for this approach.

Chemotherapy scheduling – 'dose-dense' therapy

There is increasing evidence that by delivering dose-dense, or dose-intense treatments, drug resistance can be partially overcome, resulting in an improvement in response rate and survival. Higher response rates of up to 46% have been achieved with the dose-intensive regimen of weekly cisplatin plus daily oral etoposide [33]. Much of the data on dose-dense therapy for recurrent ovarian cancer are found in phase II studies and retrospective series from single institutions. Rose and colleagues conducted a study in 28 patients, using weekly paclitaxel and three-weekly carboplatin, in platinum-sensitive ovarian cancer where patients had a median platinum-free interval of 12 months [34]. The regimen was found to be highly efficacious with 77% (20/26) of evaluable patients responding and 58% (15/26) achieving a complete response. Similar results have been seen in another phase II study [35] and response rates of up to 93% have been reported in retrospective audits examining outcome in platinum-sensitive patients [36], and up to 69% in a cohort of patients consisting of 'platinum-resistant' and 'sensitive' ovarian cancer [37].

Weekly low-dose carboplatin (AUC 2) and paclitaxel (80 mg/m^2) on days 1, 8 and 15 of a 28-day cycle have produced response rates of 100% [38] and 78% [39] in 'platinum-sensitive' ovarian cancer. In 'platinum-resistant' ovarian cancer a response rate of 60% and median progression-free survival of 7.9 months was reported using dose-dense weekly carboplatin and paclitaxel [40].

Interest in this approach is increasing as evidence is now emerging that dose-dense paclitaxel may also be more effective in the first-line setting. In the trial from the Japanese Gynaecological Oncology Group a significant improvement in progression-free survival and three-year overall survival has been reported [41]. If these data are confirmed in ongoing trials it would represent one of the most significant advances in treatment for 15 years.

The main toxicities with the dose-dense regimens are haematological and therefore there are often treatment delays and dose reductions. There is also the added economic and social burden of weekly treatment. Dose-dense therapy for recurrent ovarian cancer is being adopted in practice by many, but there is a need for randomised trials to determine the magnitude of the benefit of dose-dense therapy compared with other approaches.

Hormonal treatments

Tamoxifen is commonly used in the treatment of relapsed ovarian cancer, mainly when all reasonable chemotherapeutic options have been exhausted and a simple, oral and relatively non-toxic treatment that does not impact adversely on quality of life is preferred. A number of small clinical trials have demonstrated the modest benefit of tamoxifen in platinum-resistant ovarian cancer (up to 18% response rate) [42,43]. Similar results have been reported using letrozole in patients with ER-positive tumours. There was a 16% response rate and 26% had not progressed following six months of therapy [44].

Leuprorelin, a gonadotrophin-releasing hormone analogue, has also been used in patients with 'platinum-resistant' disease. A study comparing leuprorelin with chemotherapy did not demonstrate an advantage of hormonal treatment [45]. However, as no significant improvement has been seen with any agent in this setting, leuprorelin may therefore be considered as salvage therapy in selected patients.

Table 2
Open randomised trials in recurrent ovarian cancer with targeted agents

Molecular target	Drug	Chemotherapy	Number of patients	RCT	Placebo	Primary endpoint	Trial number
Platinum-sensitive relapse							
VEGF	Bevacizumab	Platinum–gemcitabine	450	3	Y	PFS	NCT00434642 (OCEANS)
VEGF	Bevacizumab	Platinum–taxane	660	3	N	OS	NCT00565851 (GOG 213)
VEGFR	Cediranib	Platinum–taxane	2000	3	Y	OS	NCT00532194 (ICON6)
Folate receptor	Farletuzumab	Platinum–taxane	900	3	Y	PFS	NCT00849667
PARP	Olaparib	Platinum–taxane	150	2	N	PFS	NCT01081951
PARP	Olaparib	Platinum-based	250	2	Y	PFS	NCT00753545 (Study 19)
PARP	Iniparib	Carboplatin–gemcitabine	41	2	N	ORR	NCT01033123
Angiopoietin	AMG 386	Weekly paclitaxel	900	3	Y	PFS	NCT01204749 (TRINOVA-1)
RAF Kinase	Sorafenib	Carboplatin–taxane	28	2	N	PFS	NCT00096200
Endothelin A	Zibotentan	Carboplatin–taxane	122	2	Y	PFS	NCT00929162
Src	AZD0530	Carboplatin–taxane	241	2	Y	PFS	NCT00610714
VEGFR	E7080	Carboplatin–gemcitabine	100	2	N	PFS Safety	NCT01133756
Platinum resistant relapse							
VEGF	Bevacizumab	Paclitaxel Topotecan PLD	300	3	N	PFS	NCT00976911 (AURELIA)
VEGF	Bevacizumab	Gemcitabine	37	2	N	PFS	NCT01131039
VEGFR	Pazopanib	PLD	54	2	N	Response Rate PFS	NCT01035658
Folate receptor	EC145	PLD	500	3	Y	PFS	NCT01170650 (PROCEED)
Folate receptor	Farletuzumab	Paclitaxel	350	2	Y	PFS	NCT00738699
PARP	Iniparib	Gemcitabine–carboplatin	48	2	N	Response rate	NCT01033292
VEGFR PDGFR C-Kit	Sorafenib	Topotecan	174	2	Y	PFS	NCT01047891 (TRIAS 2009)
Polo-like kinase	Volasertib	Topotecan or Paclitaxel or PLD or Gemcitabine	100	2	N	Disease Control Rate at week 24	NCT01121406
Angiopoietin	AMG 386	PLD	380	3	Y	PFS	NCT01281254 (TRINOVA-2)
Src	Saracatinib	Weekly Paclitaxel	102	2/3	Y	6 Month PFS	NCT01196741 (SaPPrOC)

Targeted agents

An improvement in our understanding of tumour biology has led to the identification of multiple targets and pathways crucial to cancer survival, such cell signalling pathways, mechanisms of DNA replication and repair, and angiogenesis. Numerous small molecule inhibitors and monoclonal antibodies have been developed against these targets and many are in the advanced stages of clinical development (Table 2). However, many new issues have arisen too: should targeted agents be used alone, or in combination with chemotherapy, and should targeted agents be used

as maintenance therapy? Answering these questions poses many challenges, not least because the activity of these agents may not depend on classic dose–response evaluation or response measurements for efficacy, but because there are so many agents it is difficult to conduct comparative trials. Ovarian cancer is an ideal disease to answer these as it responds well and repeatedly to a large number of anti-cancer drugs.

The angiogenic pathway has thus far generated greatest interest because of its particular relevance to ovarian cancer. Increased vascular endothelial growth factor A (VEGFA) levels have correlated with poor survival in ovarian cancer patients [46]. In addition, the VEGF pathway has been shown to be involved in the production of ascites in preclinical animal models.

The most widely tested agent is bevacizumab, a recombinant humanised monoclonal antibody that binds with high affinity to VEGFA. In recurrent ovarian cancer, two single-arm monotherapy studies with bevacizumab in heavily pre-treated patients with significant proportions of platinum-resistant patients, demonstrated very encouraging results, in terms of both response rate and progression-free survival [47, 48]. However, in one study there was significant toxicity with gastrointestinal perforation occurring in 11% of patients [48]; other toxicities included hypertension and arterial and venous thromboembolism. This has emphasised the need to appreciate the types of new side-effects caused by targeted agents and highlighted the learning-curve associated with the use of new agents compared with conventional chemotherapy drugs. These studies also underlined the importance of correct patient selection as gastrointestinal perforation was attributed to extensive intra-abdominal disease/bowel involvement and heavy pre-treatment [49].

Phase III studies of bevacizumab in first-line ovarian cancer in combination with chemotherapy and as maintenance therapy have been presented at international conferences and have demonstrated significant improvements in progression-free survival with survival data not yet mature [50,51]. In patients with relapsed ovarian cancer, there are two phase III studies in 'platinum-sensitive' tumours. The OCEANS trial is a randomised placebo-controlled study in 434 patients with bevacizumab in combination with carboplatin and gemcitabine chemotherapy followed by bevacizumab or placebo maintenance until progression [52]. This trial was recently presented at the American Society for Clinical Oncology and confirmed significant prolongation in progression free survival from the addition of bevacizumab (median PFS 12.4 months versus 8.4 months; HR 0.48; $P < 0.0001$). Another study, GOG 213, is investigating the addition of bevacizumab during and after carboplatin and paclitaxel chemotherapy and also includes a randomisation to secondary interval debulking surgery in eligible patients. The results of both these trials are eagerly awaited, as it may be that the greatest effect of bevacizumab will be seen in recurrent ovarian cancer.

In 'platinum-resistant' ovarian cancer, the AURELIA study, an open label phase III study is randomising patients between chemotherapy (liposomal doxorubicin, topotecan or paclitaxel) and chemotherapy plus bevacizumab (NCT00976911; Fig. 2). On progression, patients in the chemotherapy-alone arm have the option of crossing over to receive bevacizumab. The single agent bevacizumab phase II studies [47,48] provide a good basis for examining the activity of bevacizumab in 'platinum-resistant' ovarian cancer. An improvement in outcome for 'platinum-resistant' disease with bevacizumab could make a significant impact in this difficult-to-treat population.

Cediranib, an oral VEGF tyrosine kinase inhibitor, is being studied in combination with carboplatin and paclitaxel in ICON6, an ongoing academic phase III study in patients with 'platinum-sensitive' first relapse (NCT00544973; Fig. 3). The trial has passed through the safety stage and is now recruiting patients into the second stage. It is an important 'proof of principle' trial as it will address the question of activity of oral tyrosine kinase inhibitors in recurrent ovarian cancer as both concurrent and maintenance therapy.

Other small molecule tyrosine kinase inhibitors, BIBF 1120 and pazopanib, that target VEGFR and platelet-derived growth factor (PDGFR) receptor have been tested in phase II studies. Initial results have shown some activity [53,54], but larger-scale studies in recurrent ovarian cancer are not currently being pursued, as both these agents are being trialled in first-line therapy.

The folate receptor is highly expressed in ovarian cancer, providing an opportunity for targeted

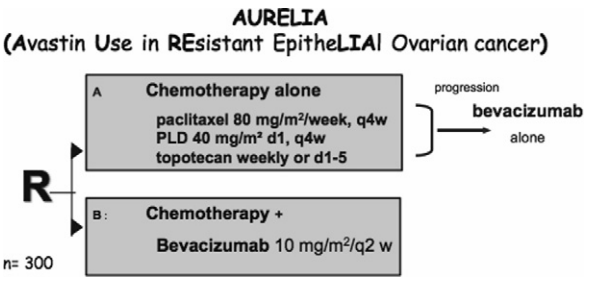

Fig. 2. AURELIA [Avastatin Use in Resistant EpitheLIAl ovarian cancer] study – bevacizumab added to chemotherapy in platinum-resistant ovarian cancer.

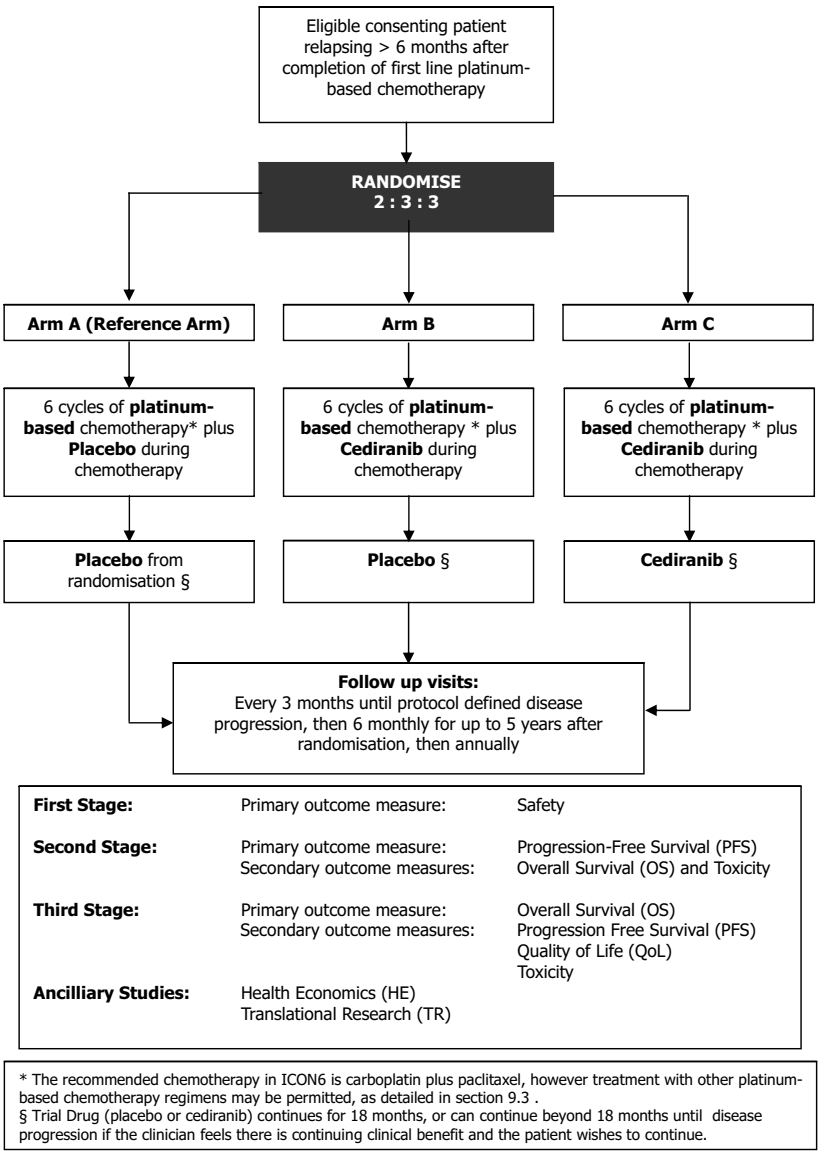

Fig. 3. ICON6 Trial Schema – cediranib in combination with platinum-based chemotherapy in relapsed platinum-sensitive ovarian cancer.

therapy. One approach is to use the antibody, farletuzumab, a humanised monoclonal antibody to folate receptor alpha. [55] A phase II study of 54 patients with platinum-sensitive relapse, who were given farletuzumab either alone or in combination with chemotherapy yielded promising results. Some patients have had a longer second remission than first remission [56]. A randomised double-blind phase III study is currently underway examining the effect of farletuzumab in combination with carboplatin and paclitaxel chemotherapy followed by maintenance farletuzumab or placebo.

Perhaps the greatest excitement has been generated by the poly (ADP-ribose) polymerase (PARP) inhibitors. PARP is a key enzyme involved in DNA damage repair and its inhibition can lead to an accumulation of double-strand breaks and cell death. Normal cells can utilise homologous recombination to repair double-strand breaks, but tumour cells deficient in BRCA1 and BRCA2 proteins employ error-prone non-homologous end-joining to repair DNA damage. Therefore, PARP inhibitors exploit the concept of synthetic lethality in cancer cells by combining drug-induced base excision repair inhibition with a defective homologous recombination DNA repair pathway [57].

The results of a landmark phase I trial using olaparib, a potent orally active PARP inhibitor, revealed a

clinical benefit of 63% in BRCA-related cancers with good tolerability [58]. Further information was gained from an international, multicentre, phase II study that assessed the efficacy of two doses of olaparib monotherapy in patients with *BRCA1/2* mutations and recurrent ovarian cancer [59]. A tumour response rate of 33% and median progression-free survival of 5.8 months was seen in the cohort of patients receiving 400 mg bid.

There is also growing evidence that PARP inhibitors have a role to play in sporadic ovarian cancers. Up to 50% of high-grade serous epithelial tumours have functional loss of proteins involved in the homologous recombination repair pathway of DNA repair [60,61]. These sporadic tumours appear to behave phenotypically like BRCA-mutated tumours, a phenomenon termed 'BRCAness' [62]. AstraZeneca Study 19 is a randomised placebo-controlled phase II study investigating the activity of olaparib as maintenance therapy in platinum-sensitive serous ovarian cancer patients who have completed treatment with two or more platinum-containing regimens [63]. This trial has shown a highly significant prolongation of progression free survival in the olaparib arm (8.4 months in the olaparib arm compared to 4.8 months in the placebo group; HR 0.35; $P < 0.00001$). The data are not yet mature for overall survival. The exact role of PARP inhibitors – there are at least eight in development for the treatment of ovarian cancer – will be defined by future phase III studies. The greatest benefit of such treatment may be in first-line and/or recurrent disease, and trials will need to be carefully designed to optimise the use of these drugs.

Src is a non-receptor cytoplasmic tyrosine kinase that is over-expressed in ovarian cancer. Src inhibition has been shown to improve the effect of paclitaxel and cisplatin in ovarian cancer cell lines and to reverse chemo-resistance [64]. Src inhibition is therefore seen as an attractive strategy for the treatment of ovarian cancer. The phase II OVERT-1 (NCT00610714) study evaluated the Src inhibitor, saracatinib, in platinum-sensitive ovarian cancer. The trial did not show any improvement in progression-free survival, but a more mature analysis is awaited [65]. A further trial, SaPPrOC, conducted by the National Cancer Research Institute in the UK, is examining the combination of weekly paclitaxel with saracatinib or placebo in platinum-resistant patients (NCT01196741).

The mTOR pathway is involved in the regulation of cell growth, proliferation and apoptosis. mTOR inhibitors have been shown to decrease cancer cell proliferation and survival. In recurrent ovarian cancer, the phase II GOG 170I study has been presented and has demonstrated modest activity of weekly temsirolimus with a 24% progression-free survival at six months [66]. Other mTOR inhibitors, such as everolimus and deforolimus are also currently involved in clinical trials.

Detailed discussion of other molecular targeted agents is beyond the scope of this review, but it is clear that there are several agents that have been shown to be active in recurrent ovarian cancer. The real challenge is to design and conduct trials that will not only confirm activity, but help to place these drugs appropriately in the pathway of the treatment of recurrent ovarian cancer.

Conclusions

The optimal treatment of recurrent ovarian cancer presents a considerable clinical challenge. Ovarian cancer often remains chemo-sensitive for two years or more following relapse. It may respond again to agents used in the first-line setting, particularly platinum compounds, or other non-platinum drugs used alone or in combination. Subtle but important gains in outcome may be achieved by selecting new schedules of treatment, such as dose-dense chemotherapy. Over the next decade many of the new drugs being studied are likely to provide even greater opportunities for therapy for relapsed disease and extending survival. Selecting the most appropriate therapy at the correct time will continue to require considerable clinical judgement.

Conflict of interest statement

J.A. Ledermann: Advisory board member of Roche, Boehringer Ingelheim, Janssen. Corporate-sponsored research: AstraZeneca. F.A. Raja: no conflict of interest to declare.

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