What are the clinical trial priorities of the future?

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Introduction

Ovarian cancer represents a paradigm for the treatment of solid tumours at the beginning of the 21st century. Multidisciplinary care is the hallmark of management, and the optimal timing of surgery in relation to chemotherapy continues to be an area of active study. However, the key obstacle to progress relates to the effectiveness of chemotherapy. Platinum-based treatment results in major tumour responses and a clear survival benefit in the majority of cases. Yet drug resistance generally develops, and as Dr. van der Zee points out elsewhere in this volume, the mechanisms for this in the clinic remain unclear. It could be argued that the best prospects for major improvements in therapy will require a better understanding of these mechanisms, and efforts in this respect are now increasing.

In parallel, clinical investigators are now pursuing a range of clinical trial options in both the primary treatment and relapsed disease settings, and these will be summarised here. It is noteworthy that many patients with advanced ovarian cancer, whose disease generally first relapses within 2 years of starting chemotherapy, can now expect at least a similar if not longer period of survival after first relapse, as a result of "salvage" chemotherapy. It is therefore important not to neglect this important phase of treatment in the consideration of future clinical trials.

First-line treatment

The addition of a third drug

A series of randomised clinical trials over the past 5 years have established the 2-drug combination of carboplatin and paclitaxel as a "standard therapy" in many centres. Some doubt has been cast on the relative contribution of paclitaxel to this regime, based on the ICON-3 [1] and GOG-132 trials [2] (described by Dr. Colombo elsewhere in this volume), and this will be discussed further in the next section. Not withstanding those concerns, many clinicians have taken the view that the best prospect for further improvement will come through the addition of a third drug which has demonstrated activity in patients previously treated with the standard doublet. A number of candidates are available, and trials (a triplet versus a doublet) are already ongoing and some completed. The addition of epirubicin (50 or 60 mg/m^2) to the paclitaxel/carboplatin combination has been assessed in 2 separate trials [3,4] (described by Dr. Colombo elsewhere in this volume), and modestly encouraging improvements in disease-free survival have been seen, albeit at the expected cost of increased toxicity. The addition of gemcitabine is similarly being assessed, and this is based on earlier very promising data from Denmark on the efficacy of the 3-drug (paclitaxel–gemcitabine–carboplatin) combination [5].

Sequential regimens

The availability of 3 (or more) drugs for first-line therapy now raises the possibility of novel treatment schedules, which might carry the advantage of introducing several non-cross-resistant agents at an early stage, but avoid the disadvantage of additive toxicity. This has led to a number of sequential treatment schedules, and they are depicted in Table 1. Also annotated are the ongoing trials which utilise this approach.

Our own group has chosen to focus on the potential importance of separating carboplatin and the taxane, i.e. avoiding concurrent treatment, since there remains a possibility that this combination could in some circumstances lead to 'antagonism' at the level of the tumour cell. Indeed, some investigators have suggested that this could be one factor to explain the counterintuitive results of GOG-132 and ICON-3. The observation that the combination does lead to a degree of bone marrow protection, particularly at the megakaryocyte level, is also not fully explained and remains of concern.

Table 1
Sequential regimes for first-line treatment of ovarian cancer

Regime	Reference	Comment
Paclitaxel–carboplatin (PC) ×6 → topotecan ×4	[6]	Pilot study confirmed feasibility. Randomised trial (AGO/GINECO) awaiting analysis
Topotecan–carboplatin ×4 → PC ×4		GOG-182 – ongoing randomised trial vs. PC ×8
Gemcitabine–carboplatin ×4 → PC ×4		GOG-182 – ongoing randomised trial vs. PC ×8
Topotecan–cisplatin ×4 → PC ×4	[7]	NCIC/EORTC – ongoing randomised trial vs. PC ×8
PC ×3 → gemcitabine/cisplatin ×2 → doxorubicin/topotecan ×2	[8]	Feasibility study
Carboplatin ×4 → docetaxel ×4 or ×12 (weekly) docetaxel CPTII ×4 docetaxel gemcitabine ×4 or ×12 (weekly) paclitaxel gemcitabine ×12 (weekly)	[9]	Ongoing Feasibility studies

The Scottish Group has therefore conducted a series of feasibility studies, which have shown that initial therapy with 4 doses of carboplatin targeted area under the curve (AUC) 7 given 3 weekly is feasible, safe and effective, and that treatment can then be completed over the next 12 weeks with various options, including docetaxel alone, docetaxel and gemcitabine, docetaxel and CPT-11 or paclitaxel and gemcitabine. Both weekly and 3 weekly taxane schedules have been assessed [9]. Currently, a 3 weekly docetaxel–gemcitabine regime looks the most promising, and an overall assessment will be made this year, as to the best candidate to take forward to a new first-line randomised trial. In addition, it is known that carboplatin and taxanes have differential sensitivity for ovarian cancer cells according to their p53 status, and it is conceivable that the best way to capitalise on this interesting difference is to treat with each drug separately, addressing wild-type p53 and mutant p53 tumour cells in turn. In these first-line trials, docetaxel has emerged as the preferred taxane, following a large (> 1000 patients) randomised trial by the Scottish Group, which demonstrated equal efficacy for docetaxel–carboplatin and paclitaxel–carboplatin, but an improved toxicity profile, particularly as regards neurotoxicity [10].

Biological agents (EGFR inhibitors)

Dr. van der Zee has provided (elsewhere in this volume) a full summary of the data which indicate that the EGF (epidermal growth factor) receptor could be an important target for a non-cytotoxic approach to ovarian cancer therapy. This pathway is under intense scrutiny in other tumour types; the two main therapeutic avenues being the monoclonal antibodies targeting the surface receptor, and the small molecule tyrosine kinase inhibitors which act at the first step in the transmembrane signal cascade. These agents are being developed both as single agents, and as modulators of chemotherapy (presumably by abrogating the survival signal attributable to the EGF pathway and enhancing drug-induced apoptosis). Results of this chemotherapy-modulation approach on other tumour types are attracting considerable attention with the most positive results in randomised trials being seen in colorectal cancer where the EGFR monoclonal antibody, cetuximab, is combined with irinotecan [11]. On the other hand, negative results in non-small cell lung cancer were seen in a large randomised trial with a combination of chemotherapy and the small molecule EGFR tyrosine kinase inhibitor, Iressa [12]. Various explanations are possible, but many investigators believe that the lack of patient selection, i.e. no prior knowledge of extent of EGFR expression or activity, was a major factor.

Experimental data with ovarian cancer cell models provide encouragement for the approach of combining platinum-based chemotherapy with an EGFR inhibitor in this disease as well, although there are a paucity of data regarding optimal sequencing.

One agent, OSI-774 (Tarceva) has been shown to have single-agent activity in refractory ovarian cancer patients [13], and judicious first-line studies combining this agent with chemotherapy are now being planned, with feasibility studies ongoing.

At present, it is conceivable that an agent such as OSI-774 could have 2 distinct roles to play in ovarian

cancer; (a) combined with first-line chemotherapy aimed at improving efficacy through a favourable shift in apoptotic signalling, and/or (b) as a single agent following chemotherapy as a means of preventing disease relapse by inhibiting an important growth signal. It will be important to address both issues in the design of future trials.

The biggest issue remains that of patient selection; how to determine on an analysis of pre-treatment tumour tissue which patients are most likely to benefit from this approach?

Ongoing trials involving OSI-774 in non-small-cell lung cancer (NSCLC) and incorporating careful analysis of EGFR expression in tumour tissue, may give further new information in this respect. At this stage, the priority will be to establish appropriate methodology to analyse tumour tissue for molecular markers of this type, and Dr. van der Zee has provided a comprehensive approach to this important area (elsewhere in this volume).

Resistance modulators

Reference has already been made to the critical importance of understanding clinical drug resistance, and one potential means for circumvention, targeting EGFR, has been described. Clearly, resistance to cytotoxic agents used in ovarian cancer is likely to be multifactorial, and a recent comprehensive review of this field is provided elsewhere [14]. While experimental data have pointed to a number of options, one area of particular interest is that of epigenetic silencing of key genes. This can result from hypermethylation, and extensive studies by R. Brown and colleagues have demonstrated the potential importance of this event in underlying resistance to platinum as well as other agents in ovarian cancer [15]. Hypomethylation, probably involving mismatch repair genes, such as *hMLH1*, leads to mismatch repair deficiency and a failure to recognise cytotoxic drug damage to DNA, e.g. formation of platinum adducts. This leads to drug resistance in ovarian cancer models. Importantly, this can be reversed experimentally, both *in vitro* and *in vivo*, by the hypomethylating agent, 5-aza-2-deoxycytidine, at doses which are themselves not toxic [16]. The question is: is this relevant clinically?

Mismatch repair deficiency can be detected in tumour cells by searching for microsatellite instability in DNA, and, fortunately, a proportion of patients with ovarian cancer do have detectable free tumour DNA circulating in serum, before and after treatment. A large-scale study conducted by the Scottish Gynaecological Cancer Trials Group has systematically examined serum for tumour DNA microsatellite instability (MSI) in patients taking part in a randomised first-line trial of carboplatin/paclitaxel vs. carboplatin/docetaxel. Preliminary data from the first 80 patients indicate a four-fold increase in MSI frequency ($P < 0.001$) at relapse compared with pre-treatment levels [17]. This provides intriguing support for the notion that mismatch repair deficiency, and hence attempts at resistance reversal with 5-aza-2-deoxycytidine (decitabine), could be clinically important. A phase I trial of decitabine with carboplatin is underway, and already it appears that, using an assay for global methylation in surrogate peripheral mononuclear cells, the combination could be a feasible one, with notionally active decitabine doses [18]. Thus randomised phase III trials of this approach merit serious consideration.

Second-line treatment

As described in the Introduction above, an important priority for the future will be to define the optimal "standard" approach to salvage chemotherapy. At present, most investigators agree that the interval since prior chemotherapy defines a watershed, at which the prospect of benefit from repeating previously given chemotherapy (particularly platinum-based) can be quite accurately defined.

Platinum-refractory

At the Royal Marsden Hospital, the watershed is 6 months. Patients relapsing before that time are treated with experimental agents if eligible for phase II trials. Examples of promising drugs tested in this context are:

ZD-473 — a novel platinum developed to circumvent drug resistance which occurs through glutathione-mediated inactivation. The drug fulfilled expectations in experimental models, with a toxicity profile very similar to that of carboplatin. However, in a phase II trial in 59 platinum-refractory ovarian cancer patients, responses were seen in only 8.3% [19].

BBR-3464 — a triplatin analogue, capable of inducing apoptosis in drug-resistant cells, independent of p53 status. In a phase II trial, no responses were seen in 18 platinum-refractory patients [20].

Epothilone B — a novel anti-microtubule agent (belonging to the macrolide family) with activity in paclitaxel-resistant ovarian cancer models. In a phase II trial (using a weekly schedule), 2 responses were seen in 50 patients with platinum-refractory disease [21].

ET-743 — (Yondelis) a novel marine compound which binds to the minor groove of DNA. Of particular interest is the combination with platinum, since ET-743-mediated apoptosis is actually enhanced by nucleotide excision repair (NER), a process which is upregulated in platinum-resistant tumour cells [22]. A phase II trial of ET-743 in 21 platinum-refractory patients indicated a response rate of 28% [23].

TLK-286 — a prodrug thought to be activated inside tumour cells by glutathione-*S*-transferase (GST), which is upregulated in some models of ovarian cancer drug resistance. A phase II trial of 31 patients with platinum-refractory disease indicated 2 patients with objective response and 12 with prolonged stabilisation [24].

Liposomal Lurtotecan (OSI-211) — a liposomal derivative of a topoisomerase-I inhibitor, designed to change the tissue distribution of the agent (pursuing the positive results obtained with the liposomal doxorubicin preparation, Doxil). phase II studies of OSI-211 are underway, following signs of activity in phase I trials [25].

Capecitabine — an oral 5-FU pro-drug. 5-Fluorouracil has established activity in ovarian cancer, but is used infrequently because of the inconvenience of intravenous (i.v.) infusion regimes. Capecitabine is now replacing i.v. 5-FU in gastrointestinal cancer because of increased convenience and equivalent efficacy. Following ingestion, the drug is activated by a 3-step pathway, the last of which involves the enzyme thymidine phosphorylase. This is present at high levels in ovarian cancer cells [26]. For these reasons, a phase II trial of capecitabine in platinum-refractory patients has been conducted, and 6 marker (CA125) responses were seen in the first 15 patients [27].

There are other active lines of investigation in platinum-refractory ovarian cancer, the most promising of which is the approach piloted by Dr. Van der Burg and colleagues [28]. This involves the combination of weekly cisplatin (given with hypertonic saline to ameliorate neurotoxicity) with oral etoposide. In platinum-refractory patients, response rates of over 40% have been reported by Van der Burg, and subsequently by Rustin's group [29]. While other studies have cast doubt on the likely impact of increasing platinum dose-intensity, a number of independent investigators have confirmed that this combination can be effective in the difficult patient group, with tolerable toxicity. Oral etoposide itself has established activity with a response rate in this group of 15–20% [30], and a clinical trial which would attract considerable support would be one which addressed the question of the extent to which weekly cisplatin adds to the activity of etoposide.

Platinum-sensitive disease

For patients whose disease relapses more than 6 months from prior treatment, many clinicians would conventionally re-treat these patients with single-agent carboplatin. Until recently, there were no data from randomised clinical trials to support an alternative approach, i.e. combination treatment. However, a recent large-scale study, described as ICON-4, does indicate that combination treatment — including re-treatment with paclitaxel together with carboplatin — can carry a survival benefit [31]. Dr. Columbo reviews this important trial in detail (elsewhere in this volume), and clinicials should be aware of the potential impact of the results. A similar study, conducted by the AGO, has randomised platinum-sensitive patients to receive single-agent carboplatin or the combination of carboplatin with gemcitabine, and the results are awaited with interest. It should be pointed out, however, that the endpoint of these trials, and subsequent treatment, will need to be scrutinised carefully. Specifically the question will arise: "is combination treatment for relapse superior to sequential use of the individual drugs as single agents in terms of overall survival and quality of life?"

Open questions

In the second-line treatment of ovarian cancer, there are other issues which remain unanswered, and certainly merit continuing attention from clinical trialists. These include:

When should the disease be re-treated? The majority of patients with ovarian cancer have detectable levels of serum CA125, and these will generally increase some 3 months or more before any signs or symptoms of disease relapse are detected. While many clinicians will correctly reserve further chemotherapy for the symptomatic patient, it is conceivable that a significant survival benefit would accrue from earlier re-treatment, and the results of an important trial coordinated by MRC/EORTC (Medical Research Council / European Organization for Research and Treatment of Cancer) will hopefully inform this important debate.

Is it the platinum-free or the treatment-free interval which is most relevant? As mentioned, most of the literature in this respect refer to the treatment-free interval as the key determinant of the likelihood of benefit from further chemotherapy [32]. However, an increasing body of opinion takes the view that the platinum-free interval deserves further attention. In other words, a patient relapsing within say 3 or 4 months of carboplatin-based treatment, who is then re-treated with another agent, e.g. liposomal doxoru-

bicin, and then relapses again 6 months later, may become eligible for carboplatin again since the interval from prior carboplatin may now be longer than 12 months. Data from one non-randomised study would support this notion of a further consideration of the platinum-free interval [33]. These are important clinical considerations, and the field would benefit from further trials which help to define further the potential of repeated carboplatin exposure.

How can we optimise the use of currently available second-line agents, e.g. liposomal doxorubicin, topotecan? Currently, the clinician has a range of options open to him for relapsed disease, and as mentioned previously, one of the most important relates to the potential for carboplatin re-treatment. When this is not an option, the judicious use of other agents can be of significant benefit, and again this offers a number of clinical trial opportunities. These include:

For liposomal doxorubicin: how can the incidence of skin toxicity be reduced, is there a role for steroids, or pyridoxine?

For topotecan: can an easier or lower dose schedule be defined; is 3-day treatment satisfactory?

Maintenance chemotherapy

Until fairly recently, the notion that continued treatment with chemotherapy could be beneficial after patients had obtained their best response to induction treatment (generally with 6 cycles of chemotherapy) attracted little support from clinicians. Published trials, usually involving continued platinum-based therapy, were generally negative. However, a recent US-based trial, in which patients after achieving best response to paclitaxel–carboplatin were randomised to either 3 months or 12 months of continued 3 weekly cycles of paclitaxel, has changed perceptions in the minds of some oncologists [34]. The trial was stopped earlier than planned, after the accrual of 250 patients, because an interim analysis showed a significant difference in the recurrence rate in favour of the 12-month arm, despite increased (neuro) toxicity in that arm. The numbers of relapses in the 2 arms were 34 and 20 respectively. No overall survival difference was found, and several investigators have pointed to the danger of forming major conclusions on the basis of such a small number of treated patients. Nevertheless, the trial has served to re-awaken interest in the field of maintenance chemotherapy, specifically with the agent paclitaxel. Since the drug does possess anti-angiogenic as well as cytotoxic properties, further studies — preferably placebo-controlled — are certainly justified.

High-dose and intraperitoneal chemotherapy

For many cytotoxic agents, drug resistance can be overcome experimentally by increasing exposure at the target tumour cell. This can be achieved in the clinic in ovarian cancer in 2 ways: (a) by high-dose i.v. delivery with various manoeuvres to protect bone marrow (e.g. peripheral blood stem cells mobilised by GM-CSF (granulocyte macrophage colony-stimulating factor)); or (b) by intraperitoneal chemotherapy which permits high drug concentrations to be achieved in the vicinity of tumour cells that frequently lie within the peritoneal cavity. Both approaches remain areas of active clinical research.

For high-dose i.v. chemotherapy, there is a paucity of proper randomised trial data. One trial has reported a survival benefit for the approach when compared with standard dose treatment as a consolidation treatment, but the numbers treated were small and the long duration of the trial points to the difficulties of patient accrual [35].

For intraperitoneal (i.p.) chemotherapy, 3 large-scale randomised trials in the U.S. have reported an advantage when treatment was given as part of first-line therapy, but there were questions over trial design in 2 of the 3, with inequalities in dose intensity in the treatment arms [36–38]. Nevertheless, the i.p. approach remains an active area for future clinical trials, not least because of the wealth of novel agents which might utilise this approach. Studies on solid peritoneal deposits indicate only limited drug penetration from the peritoneal surface, indicating that the approach may be best reserved for patients with microscopic residual disease.

Imunotherapy and radio-immunotherapy

As the results of conventional chemotherapy appear to have reached a plateau, other approaches have been explored and 3 examples of ongoing randomised trials are given. Interferon is a widely used agent, with an established role in renal cancer, but its single agent activity in ovarian cancer is negligible. However, it can enhance the activity of cisplatin in experimental ovarian cancer models, and a remarkable benefit was seen in one randomised trial when gamma-interferon treatment was added to conventional platinum-based treatment [39]. This combination is therefore being reassessed in a new larger-scale trial.

An alternative immunotherapeutic approach is to target the CA125 antigen which is widely expressed on ovarian cells. A monoclonal antibody which targets CA125 has been found in a clinical trial to

stimulate a significant immune response (T cells and APC (antigen-presenting cells)) following i.v. administration [40]. Patients receiving this antibody (after completion of conventional treatment) who demonstrated the most profound immune response appeared to have the best survival, and this has led to further randomised trials.

A third approach, i.e. radio-immunotherapy, utilises the i.p. route to deliver a monoclonal antibody bearing a therapeutic dose of the beta particle emitter Yttrium-90, targeting the MUC 1 antigen on ovarian cancer cells [41]. Again, an ongoing randomised trial is evaluating this approach, following an earlier non-randomised trial which suggested a survival benefit.

Other novel approaches

Ovarian cancer is a particularly fertile area for developmental therapeutics. Dr. van der Zee has comprehensively covered potential advances in genetic therapy (elsewhere in this volume) and, clearly, delivery issues will be crucial here. Further developments in targeted therapy are foreseen in a number of areas, and novel cytotoxics should not be neglected. These include a novel quinazoline-based thymidylate synthase inhibitor, designed to enhance specificity through its affinity for the alpha-folate receptor which is now known to be highly expressed in ovarian cancer [42]. A wide range of other molecularly targeted agents are being actively explored in preclinical and early clinical studies. Those particularly relevant to ovarian cancer are inhibitors of the PI3 (phosphatidylinositol 3) kinase/Akt pathway, since abnormalities in this pathway have been noted in ovarian cancer cells. Other interesting and novel molecular targeted agents include inhibitors of the molecular chaperone, HSP90. The example most advanced in clinical (phase I) trials is an analogue of geld-anamycin, 17 allyl amino geld-anamycin (17AAG). The importance here is that several intracellular signals which impact on response to key drugs, such as taxanes and platinum, are affected by drugs such as 17AAG [43]. Thus, the combination of this agent with cytotoxic agents will be a high priority for future trials.

An alternative approach to novel cancer therapy focuses on angiogenesis, and includes monoclonal antibodies and small molecules which target key receptors such as VEGFR (vascular endothelial growth factor receptor). The particular relevance in ovarian cancer relates to data which show that increased VEGFR expression is linked to the production and maintenance of ascites [44].

Summary

In this article, a number of areas for future activity in clinical trials in ovarian cancer have been identified. These include:

- The addition of a third drug to a conventional doublet in first-line treatment, particularly using novel sequential schedules.
- The addition of EGFR inhibitors to conventional chemotherapy as part of first-line treatment.
- The evaluation of resistance modulators, specifically decitabine, in combination with carboplatin.
- The evaluation of novel agents in platinum-refractory relapsed patients.
- The evaluation of weekly cisplatin/etoposide in platinum-refractory relapsed patients.
- The further evaluation of combination chemotherapy versus single agent treatment in platinum-sensitive relapsed patients.
- The optimal timing of chemotherapy for relapse.
- The role of maintenance chemotherapy (with paclitaxel).
- The true role of i.p. chemotherapy.
- The evaluation of various forms of immunotherapy and radio-immunotherapy.
- The evaluation of novel molecularly-targeted agents.

Entry of patients with ovarian cancer into clinical trials must be a high priority for all those involved in the care of these patients; their families, as well as future generations, should expect nothing less.

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