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Future directions for the management of ovarian cancer

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Abstract

Although the results of treatment of ovarian cancer have improved over the past 20 years with the introduction of platinum and more recently taxoid-based chemotherapy, the majority of patients still die of this disease. Further improvements may be expected by the incorporation of other new agents in more imaginative schedules, perhaps including a sequential approach or neoadjuvant regimens. Other experimental approaches that show promise include intraperitoneal treatment, e.g. genetic therapy. A better understanding of the mechanisms underlying clinical drug resistance will be important in the rational development of a number of exciting approaches aimed at overcoming this key obstacle.

Keywords: Ovarian cancer; Chemotherapy

1. Introduction

Current first-line chemotherapy for advanced ovarian cancer can result in response rates of 70–80%, median progression-free survival of 16–22 months and 5-year overall survival of 20–30%. The majority of women therefore continue to die of this disease because of recurrent, drug-resistant cancer. New, non cross-resistant agents are needed for more effective salvage therapy and for inclusion into better first-line treatment regimens.

In order to incorporate these into improved treatments of ovarian cancer, a variety of approaches are currently being addressed in clinical trials. These include:

a. Novel three drug concurrent or sequential chemotherapy regimens
b. Re-assessment of the potential value of maintenance chemotherapy
c. Neoadjuvant chemotherapy with/without interventional debulking surgery
d. Re-evaluation of the role of intraperitoneal chemotherapy
e. Other emerging areas of research include experimental modalities, such as dose intensification, gene therapy, modulation of chemosensitivity and targeting the processes of angiogenesis and metastasis.

2. Combination therapy options

Several drugs have shown activity against platinum-pretreated ovarian cancer, suggesting the possibility in some cases of using them in combination with platinum–paclitaxel as part of first-line schedules. These include: anthracyclines (e.g. epirubicin [1] and Caelyx® [2]); topoisomerase inhibitors (e.g. etoposide [3], topotecan [4]); antimetabolites (e.g. gemcitabine [5]); vinca alkaloids (e.g. vinorelbine [6]); and alkylating agents (e.g. treosulphan [7]). The options are either to make up a combination of three drugs to be given concurrently, or to administer them in one of several sequential options. For example, the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Studiengruppe Ovarialkarzinom recently evaluated the three-drug combination of epirubicin–paclitaxel–carboplatin (ET-Carbo) and in a phase I/II study were able to demonstrate the safety of the regimen of epirubicin 60 mg/m^2, paclitaxel 175 mg/m^2 as 3-h infusions and carboplatin area under concentration curve (AUC) 5 (ET-carbo). A subsequent randomised trial comparing ET-Carbo with carboplatin–paclitaxel has recently been completed by the same group; disappointingly, the preliminary results indicate no clear benefit for the addition of epirubicin [8].

Hansen and co-workers [9] showed that combination therapy with gemcitabine, paclitaxel and carboplatin also appeared to be a feasible and very active option. In a pilot study of 24 previously untreated patients, the

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response rate to the three-drug combination was 100%, even though 14 of these had bulky disease. Treatment comprised gemcitabine, 800 mg/m^2 on days 1 and 8, carboplatin AUC5 and paclitaxel 175 mg/m^2 (3 h). Dose-limiting toxicity was haematological (both Grade IV neutropenia and thrombocytopenia), but this was generally uncomplicated. Randomised trials in which this three-drug combination is one option are ready to begin both in Europe and North America.

2.1. Caelyx® combination therapy

A number of phase I studies are underway looking at combining liposomal doxorubicin (Caelyx®) with several different drugs active in ovarian cancer, including: paclitaxel, cisplatin, topotecan and gemcitabine. The initial combination of Caelyx® with paclitaxel indicated that Caelyx® 40 mg/m^2 elicited skin and oral toxicities when combined with doses as low as 90 mg/m^2 of paclitaxel [10]. When the Caelyx® dose was decreased to 30 mg/m^2 escalation of paclitaxel to 135 mg/m^2 was possible without major toxicities. A recent study indicates a pharmacological interaction between paclitaxel and Caelyx®, so that the clearance of Caelyx® is decreased in the presence of weekly paclitaxel [11]. The New York Gynecologic Oncology Group has utilised this combination (with paclitaxel being given weekly) in a phase II study of endometrial cancer. The preclinical data suggest that the combination is active, with a response rate exceeding 50% (G. Hornreich, data not shown). Other two-drug combinations involve Caelyx® together with cisplatin, topotecan or gemcitabine. In general, these indicate that virtually full doses of Caelyx® may be given, with dose-limiting toxicity being mainly haematological. A three-drug combination of Caelyx® and including paclitaxel together with cisplatin has recently been reported [12], as well as one including carboplatin [13]. Cumulative toxicities may prove to be problematic using a 3-week cycle for Caelyx® in concurrent schedules; a sequential schedule may eventually prove to be more feasible.

2.2. Sequential or concurrent therapy?

The use of combination therapy has expanded the options available for treatment of ovarian cancer, but consideration has to be given to the development of drug resistance. In trying to avoid this problem, a number of approaches have been considered. A sequential regimen is one option, involving the use of one agent at maximal dose first to achieve maximal kill and then switching to a second drug or combination to eradicate any cells that may have developed resistance to the initial treatment. Such studies, although proven positive in randomised trials in other cancers such as breast [14], have not been conducted (extensively) in ovarian cancer. Logically, such an approach should prove effective. Laboratory data indicate that the sensitivity of tumour cells to paclitaxel and cisplatin differs substantially according to their molecular characteristics; those with mutant or dysfunctional p53 may be hypersensitive to paclitaxel [15], in contrast to cisplatin, to which such cells are generally resistant [16]. Sequential therapy with these two drug classes may make the best use of these differences. A feasibility study of a sequential schedule comprising single-agent carboplatin followed by the combination of a taxoid with gemcitabine is now underway under the aegis of the Scottish Gynaecological Cancer Trials Group.

Other sequential approaches have incorporated topotecan, which is now the subject of a randomised clinical trial in the AGO, in which patients receive sequential single-agent topotecan after conventional paclitaxel–carboplatin chemotherapy. This follows the successful completion of a feasibility trial of this approach [17].

3. Maintenance therapy

Randomised trials of maintenance therapy have generally proved negative in ovarian cancer [18]. However, the conduct of these trials has been hampered by the development of cumulative side-effects with protracted use, e.g. nephropathy and neuropathy for cisplatin. This may not necessarily be the same for paclitaxel, and an argument in favour of its potential as maintenance therapy (perhaps at lower doses) is its demonstrated anti-angiogenic activity. Randomised trials of this approach are underway in the US.

Maintenance, or consolidation, therapy can also involve approaches other than chemotherapy. These include the use of targeted radiation therapy, e.g. the intraperitoneal administration of the beta particle emitter Yttrium-90, bound to a monoclonal antibody (HMFG1), which recognises the membrane antigen MUC1. Although an initial report of a randomised trial of this approach—given as consolidation to responding patients following intravenous (i.v.) chemotherapy—was described as negative [19], longer-term follow-up will be necessary before definitive assessments can be made because of the small number of patients randomised.

Various forms of immunotherapy have also been evaluated in the context of maintenance therapy. For instance, an interesting recent report on a trial using an i.v. administered monoclonal antibody with high affinity for CA125 (designed to mobilise tumour-specific immunity) indicated a high degree of correlation between survival and the extent to which various immune parameters had been affected [20]. Further follow-up on this study will be particularly interesting.

4. Neoadjuvant chemotherapy with/without interval debulking surgery

Clinicians largely agree that the optimal management of ovarian cancer involves both platinum-based chemotherapy and cytoreductive surgery conducted by specialist surgeons. Conventionally, surgery has been carried out first, followed by chemotherapy, but there is a rationale for reversing this order. Initial (neoadjuvant) chemotherapy could eradicate a proportion of tumour cells, rendering cytoreductive surgery both easier and more effective, perhaps by removing surgically those resistant tumour cells which could not otherwise be dealt with successfully.

In this context, the potential value of interval debulking surgery has been evaluated in two prospectively randomised trials. A European Organization for Research and Therapy of Cancer (EORTC) trial on 278 patients who had responded to three courses of cisplatin/cyclophosphamide (PC) compared standard treatment (a further three courses of PC) with interval surgery followed by three courses of PC [21]. In the latter group, complete removal of all macroscopic tumour could be achieved in 8% of patients and a further 29% had tumour residuals of $\leqslant 1$ cm. In addition, median survival was prolonged by 6 months, indicating a clear advantage for interval debulking. The other trial was much smaller, involving 86 unselected ovarian cancer patients with tumour residuals $>$ 2 cm following primary surgery and was terminated prematurely [22]. Platinum-based chemotherapy alone was compared with chemotherapy, followed by interval debulking and further chemotherapy. The median survival interval for the intervention debulking surgery group was 15 months (95% Confidence Interval (CI): 10–20 months) and for chemotherapy alone was 12 months (95% CI: 8–16 months); the difference although not significant suggests a positive trend in favour of debulking surgery.

Two confirmatory trials for the approach of interval debulking are on-going: one in the US (Gynecologic Oncology Group (GOG)) and one in Europe (ICON Collaboration, UK). Interval debulking surgery may well be appropriate in patients whose disease is responding or stable (non-progressive) during induction chemotherapy. For the future, an important issue is whether these data can be extrapolated to a more widespread use of neoadjuvant chemotherapy, in patients with bulky, but operable disease. A randomised trial of this approach is now underway within the EORTC.

5. Intraperitoneal chemotherapy

Intraperitoneal chemotherapy offers the potential pharmacological advantage of exposure of tumour cells to higher doses of chemotherapy than could have been achieved systemically. A 6-month survival benefit with intraperitoneal cisplatin plus i.v. cyclophosphamide over standard PC therapy was shown in an American Intergroup trial in patients with minimal residual disease [23]. A second trial, GOG 114, compared i.v. cisplatin/paclitaxel with i.v. carboplatin, followed by intraperitoneal cisplatin plus i.v. paclitaxel and again showed improved progression-free survival in the intraperitoneal arm: 28 months versus 23 months [24]. However, toxicity in the intraperitoneal arm was considerable and an overall survival benefit was not shown. In addition, the trial design was flawed because of the i.v. administration of carboplatin in the intraperitoneal arm. As a consequence, the trial is being repeated with an improved design.

At this stage, intraperitoneal chemotherapy remains an experimental approach, but it still has promise, not least for the taxoids as well as cisplatin.

6. Experimental approaches

6.1. Dose intensification

The use of high-dose chemotherapy supported by peripheral stem cells has been studied as a means of overcoming drug resistance in a number of feasibility studies. For example, a 2-fold dose intensification in 42 patients involved cisplatin 100–150 mg/m^2 (days 1 and 2), doxorubicin 80–100 mg/m^2 (days 1 and 2) and cyclophosphamide 1.6–2.4 mg/m^2 (days 1 and 2); treatment interval was 6 weeks [25]. The 5-year survival rate for 22 patients without evidence of disease at initiation (R_0 resection) was 78% compared with just 26% in patients with post-operative tumour residuals.

Clearly, the approach is feasible, but any claims for improved efficacy await the outcome of ongoing randomised trials. The best prospect may be in patients with minimal residual disease following induction chemotherapy. In this respect, the results of a recent randomised trial conducted in France are particularly interesting [26]. Patients who had achieved complete remission after conventional chemotherapy were randomised to receive high dose chemotherapy with carboplatin and cyclophosphamide or else three further courses of conventional dose treatment. After 36 months (median) follow-up, there is a significant difference in median disease-free survival (22 months versus 11 months, $P = 0.03$), favouring the high-dose arm.

The French trials group are planning to proceed to a further study using tandem (two successive) high-dose procedures. While the approach is clearly of interest, it should be noted that trial accrual has been extremely slow (110 patients over 5 1/2 years) and this perhaps reflects the high degree of selection needed when considering patients for this approach.

6.2. Genetic therapy

Genetic therapy for cancers has so far failed to live up to expectations, partly because delivery issues in the clinical setting present a formidable obstacle. Ovarian cancer offers the opportunity to investigate this approach through intraperitoneal therapy, because of the propensity of this disease to remain confined to the abdominal cavity. One approach studied in phase I trials is the use of the adenovirus, Onxy-015, attenuated so that it replicates selectively in cells with absent or non-functional p53 [27]. This may be a particularly appropriate target in ovarian cancer, as p53-mutant cells are known to be strongly associated experimentally with drug resistance, particularly to cisplatin [25].

In a phase I trial in 15 patients with ovarian cancer, intraperitoneal administration of Onyx 015 led to a greater degree of toxicity than had previously been observed when the virus had been given intratumorally in head and neck cancer patients. However, virus replication was seen in one patient in peritoneal washings taken following treatment [28].

A complementary approach has been to re-introduce wild-type p53 back into tumour cells in an attempt to restore chemosensitivity and to stimulate apoptosis. This has been achieved using adenoviral vector delivered intraperitoneally [29]. A large-scale, randomised trial is now assessing the potential of this approach in combination with platinum-based chemotherapy.

In addition, clinical trials have been conducted using the EIA adenoviral protein, which induces apoptosis in tumour cells through a variety of mechanisms. phase I trials of intraperitoneal therapy have demonstrated the feasibility of this approach [30] and phase II trials in ovarian cancer are underway.

6.3. Modulation of chemoresistance

Clinical drug resistance in ovarian cancer is a major obstacle, and the underlying mechanisms have not yet been clarified. One possible candidate is overexpression of P-glycoprotein. This energy-dependent membrane pump is the basis of so-called 'multidrug resistance', which relates to certain natural product drugs including taxoids. P-glycoprotein has been detected with variable frequency in ovarian tumour biopsies and appears to correlate with poor prognosis [31]. PSC833, a non-immunosuppressive analogue of cyclosporin A, has been studied as a means of reversing the effects of P-glycoprotein. One study combined PSC833 with paclitaxel in patients with paclitaxel-refractory ovarian cancer [32]. Results indicate a pharmacokinetic interaction, probably based on PSC833-inhibition of paclitaxel clearance; hints of clinical antitumour activity were also seen. A large scale randomised trial of first-line therapy with paclitaxel/carboplatin with/without PSC833 was started in 1999.

An increase in drug sensitivity has been achieved experimentally by certain signal transduction inhibitors, such as inhibitors of epidermal growth factor (EGF)-receptor tyrosine kinase. Interestingly, one of these agents (OS1-774) also shows evidence of clinical activity as a single agent in refractory disease [33]. Its use, both in combination with chemotherapy and as monotherapy, is therefore under study. A correlation between taxoid resistance and high level of expression of Raf-1-kinase has been observed experimentally [34] and this may have increasing relevance in ovarian cancer as first-line taxoid treatment becomes the norm.

Another potential mechanism underlying clinical drug resistance could be so-called mismatch repair deficiency. Experimental data indicate that deficiency of certain key enzymes, particularly hMLH1 (due to gene hypermethylation) leads to failure of cell death following exposure to cytotoxics through 'replicative bypass', by which DNA damage is not recognised and cells continue to divide [35]. The clinical relevance of this can be assessed by analysing tumour DNA (present in serum) for microsatellite instability. Such an approach is underway in a large-scale Scottish Gynaecological Trial Group study (SCOTROC). Importantly, hypomethylating agents, e.g. 5 aza-2-deoxycytidine can reverse resistance experimentally and clinical trials of this approach are also planned [36].

6.4. Angiogenesis and metastasis

Angiogenesis, invasion and metastasis are central to cancer development and novel therapies are being developed to target these processes. An integral part of invasion is the degradation of extracellular matrix and inhibitors of matrix metalloproteinases (MPP), the enzymes responsible for such degradation, are being researched. These vary considerably in specificity for different isoenzymes and their clinical potential will soon become apparent with the conclusion of several randomised clinical trials.

A range of other cellular signals and growth factors are involved in the stroma–tumour cell interaction which gives rise to angiogenesis, and one of these vascular endothelial growth factor (VEGF), is particularly relevant in ovarian cancer. VEGF is, in fact, secreted by ovarian cancer cells and is an important factor in the generation of ascites. Experimentally, significant shrinkage of intraperitoneal tumour can be achieved in a murine model of ovarian cancer using an anti-VEGF receptor antibody. Phase I trials of small molecule VEGFr tyrosine kinase inhibitors are well underway, and their evaluation in ovarian cancer will be particularly important, acknowledging that a proper assessment of their role will require randomised trials which may need to be lengthy and of considerable size.

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