REVIEW ARTICLE

Drugs 2008; 68 (6): 771-789
0012-6667/08/0006-0771/$53.45/0

Pharmaceutical Management of Ovarian Cancer

Current Status

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Abstract

Over recent decades, truly impressive progress has been made in the outcome associated with the pharmacological antineoplastic management of women with advanced ovarian cancer. Following initial surgery, the large majority of patients with this malignancy will receive a chemotherapy regimen that includes a platinum drug (carboplatin or cisplatin) and a taxane (paclitaxel or docetaxel). Currently, objective responses are observed in approximately 60–80% of patients treated in the front-line setting, with documented improvements in overall survival compared with prior non-platinum and taxane programmes. Unfortunately, despite the high response rate to initial chemotherapy, the majority of women with advanced disease will experience recurrence of the malignant process and be

candidates for a variety of possible second-line therapeutic options. It is well recognized that ovarian cancer patients who are documented to experience an initial response to platinum-based chemotherapy but where the disease recurs approximately 6 or more months following the completion of primary therapy, may have another clinically meaningful response (both objective and subjective) to a second platinum-based strategy. However, an optimal management approach in this setting remains to be defined. Furthermore, the malignant cell populations in all ovarian cancer patients who experience an initial relapse of the disease process will eventually be resistant to the platinum agents. In this setting, multiple drugs have been shown to be biologically active. Again, an optimal strategy to be employed in the platinum-resistant setting has yet to be demonstrated through the conduct of evidence-based trials. Reasonable goals of therapy in women with recurrent or resistant ovarian cancer are to improve overall survival, reduce the severity (and delay the occurrence) of symptoms and optimize overall quality of life.

1. A Long History of the Administration of Antineoplastic Agents in the Management of Ovarian Cancer

For more than 50 years, epithelial ovarian cancer has been recognized to be one of the most biologically sensitive solid tumours to cytotoxic chemotherapeutic agents.[1] During the earliest days of the modern chemotherapeutic era, the newly identified alkylating agents were examined as therapeutic strategies in this malignancy.[1,2] Although the definitions of clinical activity were not as clearly delineated during this time period as they are today, it was evident that palliation of distressing symptoms (e.g. abdominal pain resulting from malignant ascites accumulation) was achieved in a substantial percentage of individuals treated with several drugs (melphalan, thiotepa, cyclophosphamide) in this therapeutic class.[3]

Unfortunately, most of these responses were relatively short lived. Moreover, long-term follow-up revealed that a subset of ovarian cancer patients who received alkylating agents for extended periods of time as a result of impressive control of the malignant process, ultimately died as a direct result of developing treatment-induced secondary acute myelogenous leukaemia.[4-6] Not surprisingly, this profoundly disturbing experience has appropriately tempered enthusiasm for any form of 'maintenance therapy' in ovarian cancer.

Additional cytotoxic agents developed during this era, including doxorubicin, methotrexate, altretamine and fluorouracil (5-FU), were subsequently shown to possess at least a modest degree of biological activity in ovarian cancer.[3,7] As a result, single-agent treatment of ovarian cancer (e.g. oral melphalan) was largely replaced with combination chemotherapy regimens, such as Hexa-CAF (altretamine, cyclophosphamide, doxorubicin and 5-FU) and AC (doxorubicin and cyclophosphamide).[7-9] Limited phase III trial data confirmed that combination therapy could improve objective response rates compared with single alkylating agents, but the overall impact on survival was more modest.[8]

2. Primary Chemotherapy

2.1 The Cisplatin Era

In the 1970s, cisplatin, one of the most toxic pharmaceutical agents ever delivered to any patient (neurotoxicity, emesis, nephrotoxicity, ototoxicity), was introduced into the clinic.[10-13] However, this drug, with its impressive list of distressing adverse effects, was reluctantly accepted (by patients and oncologists) because of the recognized remarkable

level of both biological and clinically relevant activity of the agent in multiple tumour types, including ovarian cancer.[14-16]

Cisplatin was initially revealed to produce objective responses in women with ovarian cancer whose disease was shown to be resistant to alkylating agent therapy.[15,16] Of note, during this era, the definition of 'resistance' varied, and essentially included all patients whose cancers recurred or progressed following initial therapy.

Following this experience, cisplatin was quickly moved to the front-line setting[17-20] and the agent subsequently became established as the cornerstone of the chemotherapeutic management of ovarian cancer. Both individual phase III randomized trials and several meta-analyses involving the results of multiple studies, have revealed the platinum agents to be the single most active class of antineoplastic drugs in this malignancy.[17-21]

2.2 Cisplatin-Based Combination Chemotherapy

For a period of time there existed considerable controversy regarding the 'optimal' cisplatin-based, multi-agent regimen, with individual phase III trial data supporting the two-drug combination of cyclophosphamide plus cisplatin,[22-24] but with several meta-analyses suggesting the superiority of a three-drug regimen of cyclophosphamide, doxorubicin and cisplatin.[25-27] Ultimately, most investigators became convinced that any possible small benefit resulting from the addition of an anthracycline to the two-drug cisplatin plus cyclophosphamide regimen was outweighed by the well recognized additional toxicity associated with such a strategy.[28]

2.3 Carboplatin-Based Chemotherapy

Initially proposed as a more active platinum drug, carboplatin has been shown in multiple phase III randomized ovarian cancer trials to be equivalent in efficacy to cisplatin, but to possess a substantially superior adverse effect profile, particularly a lower risk of severe emesis, nephrotoxicity and neurotoxicity.[29-33] A specific highly appealing feature of carboplatin compared with cisplatin, is the ability to easily deliver the drug in the outpatient setting, without the requirement for extensive hydration to prevent the nephrotoxic effects of the parent drug.

Also, in general, the well recognized dose-limiting haematological toxicity of carboplatin produces less severe clinically relevant consequences to patients and is easier to manage (e.g. dose reduction, use of bone marrow colony-stimulating factors) than are the adverse effects associated with cisplatin. Furthermore, compared with cisplatin, it has proven easier to combine other active antineoplastic agents in ovarian cancer with carboplatin (e.g. paclitaxel).[31-34]

However, it is important to again note that the almost universal choice of carboplatin for intravenous administration in the management of ovarian cancer, rather than cisplatin, is based on a more favourable toxicity profile and ease of delivery, and not on any evidence of superior efficacy.[29-34]

2.4 Platinum Plus Taxane-Based Primary Chemotherapy

In the late 1980s, paclitaxel was demonstrated to be an active agent in platinum-resistant ovarian cancer.[35-37] In this era, the definition of 'primary chemotherapy resistance' in ovarian cancer had become reasonably well standardized to include those patients whose cancers had failed to respond to initial treatment (disease progression or 'stable disease' as best response) or where an objective response had occurred, but the disease subsequently progressed within 6 months of discontinuation of platinum-based therapy.[36] Of interest, similar to the initial experience with cisplatin in ovarian cancer,[12,13] the early experience with paclitaxel suggested the drug was quite toxic,[38,39] and its continued use was justified principally by the level of biological and clinical activity observed.[35-37]

Also, similar to the drug development process for cisplatin, where evidence of activity in the second-line setting (alkylating-resistant) led to incorporation of the agent into primary chemotherapy trials,[15-17] paclitaxel was quickly combined with cisplatin in the front-line setting and directly compared with the 'standard of care' at this point in

time, which was a platinum agent plus cyclophosphamide.[21,40,41] Although several trials subsequently confirmed the superiority of a cisplatin plus paclitaxel combination in improving survival compared with the previous 'standard' of cisplatin and cyclophosphamide,[40,41] this outcome was not observed in all phase III evaluations.[21,42]

More recent evidence-based data have documented the equivalence of a cisplatin plus paclitaxel versus a carboplatin plus paclitaxel regimen employed as primary treatment of advanced ovarian cancer (table I).[31-34] Again, the carboplatin-based combination is generally preferred by most oncologists because of the ease of administration (simple outpatient regimen) and overall superior toxicity profile (less emesis, nephrotoxicity, neurotoxicity),[31-34,41,43] but the survival of patients treated with paclitaxel plus either carboplatin or cisplatin is equivalent.

A large phase III trial has also directly compared the delivery of carboplatin plus paclitaxel versus carboplatin plus docetaxel as primary treatment of advanced ovarian cancer (table II).[44] Again, the two carboplatin regimens produced equivalent survival outcomes, but the regimens were associated with quite different toxicity profiles. The paclitaxel-containing programme was associated with a modestly higher risk of peripheral neuropathy, while patients treated with the docetaxel plus carboplatin regimen experienced a moderately greater incidence of potentially clinically relevant neutropenia. There was no difference in therapy-related mortality between the two carboplatin-based approaches.

Table I. Evidence-based platinum-taxane regimens employed as primary chemotherapy of advanced ovarian cancer

Cisplatin (75 mg/m^2) + paclitaxel (135 mg/m^2 over 24 h) q21d × six cycles[34,40]
Carboplatin (AUC 6–7.5) + paclitaxel (175 mg/m^2 over 3 h) q21d × six cycles[31-34]
Carboplatin (AUC 6) + docetaxel (75 mg/m^2) q21d × six cycles[44]

AUC = area under concentration-time curve; **q21d** = every 21 days.

Table II. Strategies that failed to improve outcome in advanced ovarian cancer compared with standard dose[a] platinum plus a taxane

Extending the duration of platinum-treatment to 10–12 cycles (from 5–6)[45-47]
Modest increase in platinum-dose intensity ('double dose' platinum)[48-53]
High-dose chemotherapy[54-56]
Extending the duration of paclitaxel infusion to 96 h[57]
Adding a third cytotoxic agent (e.g. epirubicin, topotecan, gemcitabine, liposomal doxorubicin)[58-61]

a For standard doses see table I.

2.5 Additional Strategies Explored to Improve Primary Chemotherapy of Advanced Ovarian Cancer

A number of management strategies have been explored over the past decade to improve the outcome associated with primary chemotherapy of women with advanced ovarian cancer beyond that achievable with a 'standard dose and schedule' of a platinum agent (cisplatin or carboplatin) plus a taxane (paclitaxel or docetaxel) [table II].[45-61]

Unfortunately, with only a few notable exceptions (see sections 2.5.1 to 2.5.4), randomized phase III trials have failed to reveal any favourable impact of these approaches on either progression-free or overall survival in this clinical setting.

2.5.1 Unique Advanced Ovarian Cancer Populations

While previously reported clinical trial experience in ovarian cancer has included all patients with an epithelial morphology, and the general recommendation has been to treat all patients in a similar manner outside the research study setting, there is increasing data to suggest it is reasonable to consider alternative management strategies in specific subsets of the malignancy.

Primary mucinous tumours of the ovary, which comprise <5% of all patients entered into advanced disease studies, have a particularly poor survival and, in general, are quite unresponsive to platinum-based treatment.[62,63] A second very uncommon morphological subtype, clear cell adenocarcinoma, also appears to have a poor outcome when advanced at diagnosis, and although the evidence for primary

platinum-resistance is not as substantial as documented with mucinous tumours, novel approaches are unquestionably necessary in this setting.[64,65]

2.5.2 Intraperitoneal Chemotherapy of Small-Volume Residual Advanced Ovarian Cancer

Knowledge of the natural history of ovarian cancer led early investigators in the chemotherapeutic management of ovarian cancer to examine the regional route for drug delivery.[2,66,67] However, it was not until a landmark mathematical modelling study was published by Robert Dedrick and his colleagues at the National Cancer Institute,[68,69] that a comprehensive research programme exploring this novel method of drug delivery was initiated.[70,71]

A number of phase I trials documented both the safety and pharmacokinetic advantage associated with the intraperitoneal administration of several antineoplastic drugs with known activity in ovarian cancer.[70,71] This experience was followed by a series of phase II ovarian cancer regional chemotherapy trials, with most being cisplatin-based and conducted in the second-line setting.[70-72] Although surgically documented biological activity was observed in these studies, and prolonged survival documented,[73-76] in the absence of data from phase III randomized trials, it remained completely unknown if intraperitoneal treatment produced a superior impact on survival, compared with systemic administration of the same or similar regimens.

Over the past decade, three phase III trials have been conducted by US National Cancer Institute-sponsored cooperative groups that directly compared an intravenous cisplatin with an intraperitoneal cisplatin-based regimen as primary chemotherapy of 'small-volume residual' advanced ovarian cancer following an attempt at maximal surgical cytoreduction.[77-79] Although the studies differed somewhat in their specific designs (e.g. definition of 'small volume residual' disease, comparative 'control' chemotherapy regimen, agents delivered regionally with cisplatin) they all reached remarkably similar conclusions: intraperitoneal infusion of cisplatin improves overall survival when employed as primary chemotherapy (approximately 20–30% reduction in death hazard ratio) compared with systemic delivery of the agent.[77-81]

This outcome led the US National Cancer Institute in 2006 to issue a 'Clinical Announcement' to inform patients, oncologists and the public, regarding the impact of this approach on outcome in advanced ovarian cancer.[82] Research continues in this area to both reduce the adverse effects associated with regional drug delivery (e.g. examination of substituting carboplatin for cisplatin, improving catheter delivery systems, development of guidelines for use of such therapy following extensive abdominal surgery) and to possibly further enhance the favourable impact of this route of administration on survival.[83-85]

2.5.3 Maintenance Chemotherapy of Advanced Ovarian Cancer

As noted in section 1, the devastating experience with prolonged alkylating agent therapy of epithelial ovarian cancer has appropriately tempered any enthusiasm for a 'maintenance' approach to the management of this malignancy.[4-6] Furthermore, efforts to extend the number of courses of primary platinum-based treatment of the cancer have also not been shown to favourably influence outcome (progression-free or overall survival).[45-47]

However, limited non-randomized experience had suggested that prolonged administration of paclitaxel to ovarian cancer patients in the 'second-line' setting was surprisingly well tolerated, did not appear to result in new cumulative toxic effects and had the theoretical potential to exert a beneficial impact on survival.[86-88] These considerations led the SWOG (Southwest Oncology Group) and the GOG (Gynecologic Oncology Group) to initiate a phase III trial in women with advanced ovarian cancer who had attained a clinically defined complete response to primary chemotherapy, which randomized patients to either receive 3 or 12 cycles of single-agent paclitaxel (delivered on a monthly schedule at a dosage of 175 mg/m^2 as a 3-hour infusion).[89]

The study was stopped, with only one-half of the planned total patient accrual, by its Data Safety and Monitoring Committee at the time of a planned

interim analysis when a highly statistically significant favourable impact on progression-free survival was observed in favour of the 12-cycle study arm (hazard ratio 2.31; p = 0.0023).[89] This outcome was confirmed with additional follow-up of the study population, but the total sample size of the trial was insufficient to draw any conclusions regarding the impact of this novel management strategy on overall survival.[90] A confirmatory study for this highly provocative trial, being conduced by the GOG, is currently in progress.

It should also be noted that a preliminary report of a similar but not identical 'maintenance' paclitaxel regimen conducted in Italy has not demonstrated a survival benefit for the strategy.[91] In this study, ovarian cancer patients who attained either a clinically or surgically documented complete response were randomized to an observation arm or six cycles of single-agent paclitaxel, delivered at a dosage of 175 mg/m^2 every 3 weeks. Differences between this study and the previously noted SWOG/GOG trial include the smaller sample size in the Italian study (approximately 100 total patients in a 'clinical complete response' compared with 277 patients in the SWOG/GOG study) and the delivery of 'maintenance' therapy for a longer period of time in the SWOG/GOG trial (12-monthly cycles versus six cycles of an every-3-weeks schedule).

2.5.4 Chemotherapy of High-Risk, Early Stage Ovarian Cancer

Over recent decades, studies have revealed that the adjuvant administration of cytotoxic chemotherapy to women with completely resected 'early stage' ovarian cancer but with high-risk features (e.g. grade 3 tumours, positive peritoneal cytology, stage II disease),[92,93] can improve progression-free survival.[94,95] However, these studies failed to document that such a strategy would improve overall survival compared with a management philosophy that simply called for chemotherapy to be administered at the time of documented relapse of the cancer.

However, more recent data that combined the results of two relatively large phase III European studies (European Organisation for Research and Treatment of Cancer – Adjuvant ChemoTherapy on Ovarian Neoplasm trial [EORTIC-ACTION] and International Collaborative Ovarian Neoplasm [ICON-1]) of adjuvant treatment in this clinical setting revealed that the delivery of a platinum-based chemotherapy regimen following surgical tumour removal of 'high-risk' early stage ovarian cancer not only improves progression-free survival (absolute difference at 5 years 11%), but also overall survival (absolute difference at 5 years 8%).[96-100] Furthermore, a preliminary report of 10-year follow-up of one of these two studies (ICON-1) confirmed that there continues to be a statistically significant survival advantage (absolute difference 9%) for the patient population who received adjuvant treatment even a decade after the initial diagnosis.[101]

On the basis of these data, it is reasonable to conclude that the standard of care in the management of high-risk early stage disease should include the administration of platinum-based chemotherapy (most probably carboplatin based).[99,100]

Although one report has suggested it is acceptable to deliver fewer courses of chemotherapy in this setting, compared with the strategies employed in women with advanced disease (e.g. three rather than six cycles), the available evidence supports the argument that such an approach is associated with a higher risk of ultimate relapse.[102] It should also be noted that the large majority of patients receiving adjuvant chemotherapy in the ICON-1 study were treated with six cycles of chemotherapy.[101] Furthermore, it has been documented in other disease settings (e.g. breast cancer) that an inadequate number of treatment cycles can negatively impact on survival.[103] As a result, a very strong argument can be made that in the absence of contraindications to receiving a full course of platinum-based treatment (e.g. excessive emesis, development of significant neuropathy), women with high-risk early stage ovarian cancer should be treated in a manner similar to that used in the setting of advanced disease.

It is hoped that future research in this area may permit the molecular identification of those tumours that have a very low risk of recurrence, in the absence of further treatment, such that it is appropri-

ate to withhold adjuvant chemotherapy. This remains an active area of clinical research.

3. Second-Line Therapy of Ovarian Cancer

Approximately 60–80% of patients with advanced ovarian cancer will exhibit a response to primary platinum-based chemotherapy.[104] Although some of these individuals are 'cured' of their malignancy, the large majority of patients are not, and with documented recurrence of the disease process, future treatment options will need to be considered.[105]

Currently, it is interesting to note that one of the most striking features of ovarian cancer management is the existence of strong evidence-based data providing highly clinically relevant information regarding optimal treatment in the front-line setting, and the near absence of such data when the disease recurs (as unfortunately happens in the majority of patients). How should ovarian cancer patients whose disease fails to achieve a complete response, does not respond to the initial course of treatment or recurs after a period of remission, be managed?

3.1 Platinum-Sensitive versus Platinum-Resistant Ovarian Cancer

Extensive retrospective experience has confirmed that tumours of patients with ovarian cancer that exhibited an objective response to platinum-based chemotherapy may respond a second time.[106-115] It is also well established that the statistical likelihood that such a secondary response will occur will increase as the duration of the period between the completion of the prior therapy and the planned initiation of the second-line approach lengthens.[107,108,113]

As noted in section 2.4, ovarian cancer clinical trial eligibility criteria will (of necessity) quite rigidly define a patient as having either 'platinum-sensitive' (prior response to platinum and a duration of the absence of disease progression following the completion of therapy of >6 months) or 'platinum-resistant' (no response to platinum or a duration of response following completion of therapy of <6 months) disease.[36] However, in reality, the chances that an individual patient will respond a second (or third or fourth) time to retreatment with a platinum-based programme is a continuum, with the higher predicted response rates anticipated in those women with the longest time away from therapy.[107,108,113,116]

Thus, for example, available data would suggest that a patient with a 'treatment/platinum-free' interval of 9–12 months has a 20–30% probability of achieving an objective response to retreatment, while a woman who has not received the agent for a period of 32–35 months may have a predicted response rate to a second-line platinum regimen of >50–60%.[107,108,113] This information is quite relevant in decisions made regarding management options for individual patients.

Furthermore, in one specific situation, data regarding the statistical probability of achieving a biological response to second-line, platinum-based therapy in ovarian cancer can substantially influence the basic decision as to whether or not further treatment with this agent should be administrated. It is currently well recognized that approximately 10% of women with ovarian cancer who receive platinum in the second-line setting will experience clinically relevant hypersensitivity to the agent.[117-121] Although the time course and severity of these allergic reactions varies (e.g. mild diffuse rash developing several days after carboplatin treatment, or severe hypotension and respiratory compromise after a few milligrams of the drug are delivered),[117-121] and a number of investigators have documented the potential for successful continued treatment with either carboplatin or cisplatin following the demonstration of hypersensitivity,[122-127] it is also known that further use of the agent can result in the development of significant symptoms and treatment-related mortality.[117,128,129]

Thus, it is reasonable to suggest that a decision to continue platinum-based therapy in this setting should include consideration of the potential risks versus the possible benefits of this management strategy, including the statistical likelihood that clinical benefit (as measured by the objective response

rate) will occur with additional treatment employing this agent.

It is also important to note that limited retrospective data also predict that the duration of a 'secondary' platinum response will be shorter than the duration of the initial response.[114] Moreover, the duration of each subsequent response (e.g. third line, fourth line) will be shorter than previous response (e.g. second line, third line). Again, this information can be helpful in a decision to retreat with a platinum-based therapy versus employing an alternate management option.

3.2 Combination versus Single-Agent Platinum Therapy in Recurrent Disease

Until recently, it would have been most appropriate to state that single-agent carboplatin was the 'treatment of choice' when delivering a platinum-based regimen in the second-line setting.[105] This was because there was no evidence-based data supporting a favourable impact of combination platinum-based treatment, compared with single-agent treatment, in this clinical circumstance. In the absence of such data, it would be difficult to justify the additional toxicity associated with a carboplatin-based combination strategy in a palliative setting.

However, this situation has changed with the current availability of data from two phase III randomized trials that each compared a combination carboplatin-based regimen with single-agent carboplatin in women with ovarian cancer who experienced recurrence of their disease process more than 6 months following the completion of primary therapy ('platinum-sensitive' setting) [table III].[130,131]

In the initially reported study, investigators randomized patients to either be treated with a platinum regimen plus a taxane or to receive a platinum drug without a taxane.[130] Since the large majority of patients in the combination chemotherapy arm were actually treated with carboplatin plus paclitaxel, and the greatest percentage of individuals in the non-taxane containing arm were treated with single-agent carboplatin, this study has frequently, but somewhat inaccurately, been described as comparing these two approaches (carboplatin plus paclitaxel versus carboplatin alone).

Table III. Combination platinum-based chemotherapy versus single agent platinum in recurrent ovarian cancer (hazard ratios)

Regimen	Progression-free survival	Overall survival
Carboplatin plus paclitaxel versus carboplatin[a][130]	0.76 (p = 0.0004)	0.82 (p = 0.02)
Carboplatin plus gemcitabine versus carboplatin[131]	0.72 (p = 0.003)	0.96 (p = 0.735)

a The large majority but not all patients in this trial received these agents.

The second phase III randomized chemotherapy study directly compared single-agent carboplatin with the combination of carboplatin plus gemcitabine in women with platinum-sensitive recurrent ovarian cancer.[131]

As noted in table III, the paclitaxel-containing study revealed that the combination regimen produced both a favourable impact on progression-free as well as overall survival.[130] In contrast, in the gemcitabine study, although the combination regimen also showed an improvement in progression-free survival, there was no difference in overall survival between the two study arms.[131] The reasons for this quite unexpected discrepancy between the results of these two well designed and conducted trials are unknown, but may possibly relate to differences in the strategies employed in the third-line setting following documented disease progression on the protocol treatment arms between the countries participating in the different studies.

Also of interest were the specific toxicity profiles of the two combination chemotherapy strategies compared with single-agent carboplatin treatment. The 'carboplatin plus paclitaxel' regimen was shown to result in a 20% incidence of grade 2–3 neuropathy compared with only 1% in the 'single-agent carboplatin' control arm.[130] In contrast, there was no difference in the incidence of peripheral neuropathy between patients treated with carboplatin plus gemcitabine compared with carboplatin alone. The major adverse effect of the gemcitabine-

containing combination was significant bone marrow suppression.[131]

It would be reasonable to suggest that these studies provide highly relevant assistance to oncologists when they must consider therapeutic options in the setting of platinum-sensitive recurrent ovarian cancer. For an individual who has previously received a carboplatin plus paclitaxel regimen in the primary setting and has tolerated that treatment without the development of neuropathy, retreatment with carboplatin plus paclitaxel may be a very reasonable treatment approach. In contrast, if the same individual has experienced clinically evident neuropathy that either resolved or persists, the option of carboplatin plus gemcitabine may be a more appropriate management strategy.

A third option would be to sequence the antineoplastic drugs (e.g. carboplatin for 3–4 cycles, followed by paclitaxel for 3–4 cycles), rather than to deliver the cytotoxic agents in combination. The goal of such a strategy would be to reduce the adverse effects associated with combination therapy but at the same time maintain efficacy. Although this is a rational approach in carefully selected patients, it must be noted that phase III trial data do not currently exist to confirm the equivalence of sequential versus combination therapy in this clinical setting.

It is reasonable to suggest that a high priority for the academic gynaecological cancer research community should be the development of a randomized phase III trial designed to provide evidence-based guidance to clinicians managing ovarian cancer patients in the setting of platinum-sensitive recurrent disease. Unfortunately, it does not appear that such a study specifically exploring these multiple options (e.g. prospectively defined sequential therapy versus several potential combination chemotherapy regimen) is currently planned.

3.3 Chemotherapy Options in the Management of Platinum-Resistant Ovarian Cancer

A large and growing number of antineoplastic agents have demonstrated at least a modest level of biological activity when delivered as single drugs in the management of platinum-resistant ovarian cancer (table IV).[105] It is reasonable to note that several of these agents have also been examined when delivered alone in platinum-sensitive recurrent disease, but in the absence of phase III trial data it remains unknown if any such individual drug is either equivalent or superior in efficacy to a platinum agent.

There is currently no evidence-based data to state that one of these agents is better than another in regard to an impact on either progression-free or overall survival when employed as second-line treatment of platinum-resistant ovarian cancer. However, of considerable importance, recent phase III trial data have revealed that the administration of known active antineoplastic drug therapy, compared with the use of an 'inactive agent', will favourably impact survival in platinum-resistant disease.[166] In addition, extended survival (in excess of 1 year) is a highly realistic possibility even in the presence of well characterized platinum-resistant ovarian cancer.[167]

Furthermore, it is appropriate to acknowledge that in a substantial percentage of ovarian cancer patients being considered for second-line treatment, the question is really not whether to deliver 'drug A' versus 'drug B' but rather which agent should be used first. If the tumour progresses following exposure to 'drug A' then 'drug B' will be employed or the opposite sequence may be utilized. Also, follow-

Table IV. Single agents with demonstrated activity (≥10% objective response rate) in platinum-resistant ovarian cancer

Altretamine[132-135]
Bevacizumab[136-139]
Docetaxel[140,141]
Epirubicin[142]
Etoposide (oral, every 21 days)[143-145]
Gemcitabine[146-149]
Ifosfamide[150]
Irinotecan[151]
Liposomal doxorubicin[152-155]
Paclitaxel (every 3 weeks or weekly)[35-37,156,157]
Tamoxifen[158-160]
Topotecan[161-163]
Vinorelbine[164,165]

ing failure of 'drug A and drug B', it is likely that 'drug C' (also known to be active in platinum-resistant ovarian cancer) will be tried.[168,169]

A number of relevant factors should be considered when selecting second-line (and third-line, etc.) treatment strategies in the management of ovarian cancer (table V). In the absence of definitive evidence-based data to guide treatment decisions, and with the likely continued introduction of new drugs into the oncologist's armamentarium for the treatment of ovarian cancer, it can be anticipated that the complexity of the decision-making process will only increase.

4. Targeted Therapies in the Management of Ovarian Cancer

A number of the new classes of 'targeted therapeutic' agents have been examined for their potential utility in the treatment of epithelial ovarian cancer. Of interest, despite the recognized major chemosensitivity of the malignancy to classical cytotoxic agents, initial efforts to examine the utility of several targeted therapies with documented efficacy in several malignancies have somewhat surprisingly revealed these agents to be quite inactive in ovarian cancer.

Drugs that have been examined and found to exert a minimal biological influence on the natural history of ovarian cancer, despite sound preclinical data supporting their use (e.g. evidence that the presence of the 'target' negatively influences outcome and the molecular abnormality is commonly expressed in the malignancy) include agents 'targeting' the human epidermal growth factor receptor 2 (HER-2),[170] endothelial growth factor receptors[171-173] and tyrosine kinase inhibition.[174-176]

In this regard, the documented experience with trastuzumab in ovarian cancer is informative. Although early reports suggested that as many as 30% of patients with ovarian cancer overexpress the HER-2 receptor and studies suggested a negative impact of this molecular abnormalities on outcome in the malignancy,[177-179] in a clinical trial conducted by the GOG, only 11% of the large number of women screened for HER-2 overexpression were found to be candidates for treatment with trastuzumab. Furthermore, within this HER-2 overexpressing tumour study population, an objective response rate of only 7% was observed.[170]

However, recent data resulting from trials of the antiangiogenic agent bevacizumab in advanced ovarian cancer have revealed a surprising level of both biological and clinical activity for the drug when administered alone (without chemotherapy).[136-139] The response rate of 15% in several phase II trials in platinum-resistant ovarian cancer is very similar to that observed with the more active cytotoxic antineoplastic agents currently routinely employed in this clinical setting. A potential role for bevacizumab in the primary management of ovarian cancer is currently being examined in several phase III randomized trials.

A second antiangiogenic agent, aflibercept (vascular endothelial growth factor-Trap), has also demonstrated objective evidence of biological activity in women with platinum-resistant ovarian cancer.[180]

Table V. Considerations in the selection of second-line therapy for epithelial ovarial cancer

1. Prior toxicity experienced by the patient
2. Known toxicity profile of available agents
3. Presence of existing evidence-based data regarding efficacy in a particular setting (e.g. combination chemotherapy vs sequential use of cytotoxic agents in platinum-resistant disease)
4. Unique issues relevant to the individual patient (e.g. time required for regimen, family support for travel to receive therapy, available third party coverage for treatment)
5. Availability of, and eligibility for, clinical trials of interest to the patient
6. Patient choice

5. Hormonal Therapy of Ovarian Cancer

There has been a long history of the use of hormonal treatment in ovarian cancer that originated with the concept that, like breast cancer, this malignancy is strongly influenced by its hormonal environment.[181,182] However, in striking contrast to breast cancer, there currently exists extremely limited data demonstrating a role for the expression of hormonal receptors in predicting a response to a hormonal intervention in ovarian cancer, and for a major impact of this therapeutic strategy on outcome

(improvement in symptoms, prolongation of survival).[183,184]

Tamoxifen has been extensively examined both as a single agent and in combination with chemotherapy in advanced ovarian cancer. Both individual studies and analyses of multiple trials have suggested that approximately 10% of treated patients exhibit an objective response to tamoxifen delivered alone.[158-160,185] There have been no randomized trials comparing the administration of tamoxifen with cytotoxic drug therapy in the platinum-resistant setting, but a major appeal for the use of this drug is its highly favourable toxicity profile, certainly compared with cytotoxic chemotherapy. Settings where tamoxifen has been employed in the management of ovarian cancer include (i) rising CA-125 antigen level in the absence of other objective evidence of progressive disease; (ii) 'maintenance approach' in patients who have completed a chemotherapy regimen and there is a concern for a high risk of relapse; and (iii) treatment of resistant ovarian cancer, with the goal to minimize treatment-related toxicity.[185,186]

On the basis of preclinical data suggesting synergistic cytotoxicity when tamoxifen is combined with cisplatin,[187-189] this novel combination strategy has been examined in patients with platinum-resistant ovarian cancer.[190,191] Although an initial trial suggested a modest level of activity in this clinical setting,[190] these results could not be confirmed in a second study.[191]

Other hormonal agents have been investigated in this clinical setting, including leuprorelin[192] and high-dose progesterone.[193]

It is reasonable to specifically note the reported activity of letrozole examined as a second-line strategy in ovarian cancer.[194,195] In a study specifically conducted in ovarian cancer patients with estrogen receptor-positive disease an objective response rate of 16% (employing CA-125 response criteria) was observed.[195] However, it remains unknown at the present time if the biological and clinical activity of letrozole is superior to tamoxifen.

6. Chemosensitivity and Chemoresistance Assays in Ovarian Cancer Management

The profoundly successful application of *in vitro* testing to predict the effectiveness of various available antibacterial agents in individual infections led investigators to explore the benefits of such predictive strategies in the management of malignant disease. Because of the inherent chemosensitivity of ovarian cancer, and the demonstrated activity of a number of cytotoxic agents in the disease, it is not surprising that a considerable amount of research in the arena has been focused in this clinical setting.[196-202]

Tests designed to predict both the sensitivity of a particular patient's cancer to specific drugs, as well as to declare the tumour to be resistant to these agents, have been evaluated and used outside the research setting. A number of complex issues continue to plague the development of a clear interpretation of *in vitro* testing, including the fundamental question of the relationship between the cells able to grow in the laboratory setting and the actual malignancy present within a particular patient. Furthermore, as concluded in a comprehensive review of this topic by an independent panel of experts, none of the currently available tests have been shown in a well designed prospective trial to be superior to a clinician's best judgement and available evidence-based data in the selection of antineoplastic therapy.[203,204]

It is reasonable to speculate that if such studies are conducted in the future, it is possible that one or more *in vitro* testing strategies will be demonstrated to provide useful information to oncologists caring for women with ovarian cancer. However, for the present, these tests must be considered to remain in the domain of an investigative strategy or if used in the clinical setting, they should be viewed as simply one piece of data to be employed with many others in the decision to select a particular treatment option.

7. Neoadjuvant Chemotherapy

Ovarian cancer is unique among all malignancies in that it is the 'standard of care' to attempt to maximally surgically cytoreduce the cancerous masses present within the peritoneal cavity prior to the administration of chemotherapy, even when extensive disease is present at the time of initial diagnosis.[205,206] Justification for this strategy comes from extensive retrospective data demonstrating the superior survival of women who initiate chemotherapy with smaller volume residual cancer.[205-209] Unfortunately, there remain no prospective phase III randomized trials demonstrating that patients who undergo this primary attempt at surgical cytoreduction experience superior survival compared with individuals treated with chemotherapy after the diagnosis of ovarian cancer has been confirmed.

A number of gynaecological cancer research groups have reported their experience with the initial use of chemotherapy, rather than employing primary surgery, in the setting of extensive intra-abdominal ovarian cancer ('neoadjuvant chemotherapy').[210-217] Although still a controversial approach,[218] this strategy has been suggested to reduce morbidity and permit subsequent surgery ('interval cytoreduction') in patients who exhibit a major response to the chemotherapy regimen.

Fortunately, several phase III randomized trials are currently in progress that are designed to directly compare the outcome (treatment-related morbidity, progression-free and overall survival) of women with extensive intra-abdominal ovarian cancer who either undergo an attempt at a 'standard' initial debulking procedure or who first undergo neoadjuvant chemotherapy followed by interval surgical cytoreduction. The results of these trials are awaited with great interest.

8. Future Directions

The results of a number of evidence-based clinical trials have provided important information that should help guide future clinical research in antineoplastic drug delivery in the management of ovarian cancer. These include efforts to optimize and expand the benefits of regional drug delivery, further explore a role for a maintenance strategy, and investigate other targeted therapies based on preclinical identification of potentially clinically relevant molecular abnormalities in the malignancy.

It will also be important to both develop novel trial designs (e.g. increased utilization of CA-125 as a marker of progression and response[219-226]) and firmly establish reasonable endpoints for future clinical trials (e.g. progression-free survival as well as overall survival as valid primary endpoints[227]) to more rapidly introduce novel and effective single antineoplastic regimens and combination chemotherapy strategies into the management of ovarian cancer.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The author has received honoraria from Genentech, Eli Lilly and Tibutech.

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