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ADVANCED OVARIAN CANCER

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Recent advances in systemic treatments for ovarian cancer

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Abstract

Ovarian cancer remains the leading cause of death from gynaecological cancer. Advances in surgical and chemotherapeutic strategies have led to improvements in outcome. However, the majority of women present with advanced disease with little prospect for cure. In this article, we summarize the systemic management and ovarian cancer and raise a number of important issues: namely the timing of systemic therapy in relation to surgery, the selection of patients who do not require systemic therapy and the development of novel agents.

Keywords: *Ovarian cancer; chemotherapy; targeted therapy; bevacizumab; PARP inhibitors.*

Introduction

There are approximately 6000 new cases of ovarian cancer per year in the United Kingdom and the disease accounts for 4500 deaths, which represents 5% of all cancer deaths per year[1]. Most ovarian cancers are epithelial in origin and the median age at diagnosis is 63 years. Systemic treatment is only part of the effective management of ovarian cancer and the best outcomes are achieved only when there is an integration of both surgery and systemic treatment. In recent years, a number of important issues have emerged: namely the timing of systemic therapy in relation to surgery, the selection of patients who do not require systemic therapy, the development of novel agents and molecular markers that can help guide systemic treatment.

Stage I disease

Stage I ovarian cancer is curable by surgery alone in most patients. The major question that remains unresolved is which patients require systemic therapy. This issue was evaluated in two prospective randomized studies: the International Collaborative Ovarian Neoplasm (ICON-1) and the Adjuvant Treatment in Ovarian Neoplasm (ACTION) trials. These trials compared platinum-based adjuvant chemotherapy with observation following surgery in early-stage ovarian cancer. A combined analysis of the trials demonstrated a significant (8%) 5-year survival benefit favouring the adjuvant chemotherapy group[2] but beneath this result a number of questions remain. A separate analysis suggested that for those patients who were adequately staged, i.e. had lymph node sampling, omentectomy and peritoneal biopsies and therefore had truly stage I disease, there appeared to be no benefit to adjuvant chemotherapy. This was a subset analysis that involved only a minority of patients and this interpretation has therefore been criticized. Conversely, many patients, particularly those entered into the ICON-1 trial, were not properly staged and some were even known to have stage II and stage III disease. Our interpretation of the data is that the figure of an 8% benefit is probably the maximum benefit one can get from adjuvant chemotherapy in stage I disease and that if patients are fully staged, the benefit is likely to be lower, perhaps even below 5%.

There are patients who could be considered at high risk, such as: grade 3 serous tumours; suboptimal surgical staging; stage Ic; patients who have had Pfannenstiel incisions and those whose tumours have been adherent to the pelvic sidewall. Within stage 1c disease, it has been suggested that there may be differences in outcome

between tumour involving the surface of the ovaries versus pre-operative rupture and intra-operative rupture. However, numerical differences have not been shown consistently in multivariate analyses, probably due to the small number of patients in the subgroups. All these are familiar situations to the physician treating ovarian cancer and have been suggested as indications for adjuvant therapy in various analyses.

One histology subtype in particular has caused difficulty, namely patients with clear cell tumours. Clear cell stage I disease has a poorer prognosis but experience from the management of patients with advanced clear cell carcinoma of the ovary suggests that this is a relatively chemotherapy-resistant tumour. This begs the question as to whether or not adjuvant chemotherapy is likely to be of significant benefit. A recent analysis has suggested that consideration could be given to treating patients with early stage clear cell tumours with adjuvant radiotherapy after surgery[3]. For patients with stage II or stage IC disease by virtue of cytological positivity, surface involvement or unknown status of either of these, there was a significant improvement in disease-free survival in those who received radiation (relative risk 0.54; 95% CI 0.33 to 0.95; $P = 0.02$), with a 20% absolute increase at 5 years.

Finally, the issue as to whether or not taxanes should be added to platinum or whether patients should be treated with single agent carboplatin in the adjuvant setting has not been formally tested in randomized trials. There remains some controversy over the number of cycles that are required in the adjuvant setting although there is one randomized trial that attempted to address this question[4]. In the absence of robust data, many investigators have used combination platinum therapy involving taxane with the rationale that if the addition of a taxane to carboplatin is associated with a survival benefit in advanced disease, then maximal benefit in the stage I curative setting is likely to be best achieved with the combination.

Advanced disease

Platinum drugs are the most active in ovarian cancer. In the 1980s, there was controversy over whether or not other chemotherapeutic agents should be added to platinum. Two randomized trials showed an overall survival benefit[5,6] for platinum in combination with paclitaxel and one showed no such benefit[7]. Various arguments were put forward as to why there was a discrepancy between the trials but the current international standard for advanced disease has been agreed and it is 6 cycles of carboplatin area under the time–concentration curve (AUC) 5–7 over 1 h with paclitaxel (175 mg/m^2) as a 3-h infusion every 21 days. Single agent carboplatin is reserved for patients who are frail, of poor performance status or who wish to avoid the toxicities of the combination.

There has been considerable attention recently to the scheduling of carboplatin and paclitaxel and there is evidence from one randomized trial that delivering paclitaxel weekly is associated with a survival benefit[8]. A randomized trial in Europe has been launched to look at the different schedules of carboplatin and paclitaxel in advanced disease with patients being randomized to carboplatin + paclitaxel on a 3-weekly schedule, carboplatin on a 3-weekly schedule + paclitaxel on a weekly schedule or both drugs being delivered weekly.

Intraperitoneal therapy

Ovarian cancer remains confined to the peritoneum in most patients. The delivery of chemotherapy intraperitoneally has therefore been a strategy of considerable interest for many years. Several trials have reported a survival advantage for intraperitoneal (IP) chemotherapy compared with intravenous (IV) administration in women with optimally cytoreduced stage III epithelial ovarian cancer[9,10]. This approach remains controversial for a number of reasons including the potential greater toxicity of the treatment. It is considered by some to be inconvenient and many of the trial designs have been limited by the fact that the control arm is not the standard of care, i.e. IV carboplatin and paclitaxel. In addition, the dose and schedule of the two drugs have differed in the treatment arms and hence the survival advantages may be as a result of a higher cumulative dose of chemotherapy rather than route of administration. It is accepted that only patients with no macroscopic disease following surgery should be offered IP chemotherapy and most regard this strategy as only being suitable for patients in the first-line setting. There are currently a number of clinical trials underway to further address the role of IP treatment.

Relapsed disease

Patients who relapse following first-line treatment with platinum-based chemotherapy are incurable. This important fact governs how patients are managed when they relapse. Ninety percent of patients with ovarian cancer have a raised CA125 level at diagnosis and it is unusual for such patients to relapse without this tumour marker becoming abnormal before the disease is evident either on CT or in relation to the development of symptoms. A randomized trial has shown that early treatment when patients have an increase in CA125 without CT evidence of relapse or symptoms is of no benefit[11]. This raises important questions regarding how patients should be followed after first-line therapy and whether regular monitoring of the CA125 is of any use. All are agreed that when patients develop symptoms at relapse they should be considered for further treatment and the only question that remains is whether patients who have developed asymptomatic bulky disease that has clear progression should be treated before they develop symptoms or not.

Second surgery at relapse has been considered in patients who have a treatment-free interval of at least 6 months and some would suggest that surgery should only be considered if the treatment-free interval is 12 months or more. The choice of chemotherapy is dependent on the treatment-free interval as it was shown many years ago that patients with a platinum-free interval of less than 6 months are unlikely to respond to a re-challenge with platinum, whereas those that relapse over 12 months are likely to have a further good response[12]. However, this relationship is not absolute and the increasing responsiveness of relapsed disease to platinum is a continuum. Randomized trials have shown that platinum-based combinations (paclitaxel, liposomal doxorubicin, gemcitabine) are superior to single agent carboplatin for patients with so-called chemosensitive relapse, i.e. a platinum-free interval of greater than 6 months[13–15]. For example, the progression-free survival was significantly longer in patients who received gemcitabine in combination with carboplatin compared with carboplatin alone (8.6 vs 5.8 months; hazard ratio 0.72; $P = 0.003$)[15]. A further randomized trial has shown that carboplatin in combination with liposomal doxorubicin (caelyx) is superior to the carboplatin/paclitaxel combination in terms of progression-free survival[16]. The addition of a third cytotoxic agent has been investigated in randomized phase III trials and has not been shown to improve long-term clinical outcomes but is associated with increased toxicity[17]. Single agent activity for patients who have relapsed with platinum-resistant disease, i.e. with a platinum-free interval of less than 6 months is poor with active agents such as caelyx, topotecan, gemcitabine having response rates of 20% or less with progression-free survival rates of 4–6 months.

Patients with relapsed disease should be offered entry into clinical trials, particularly those with platinum-resistant tumours.

Novel agents

Targeted agents have proven successful in a variety of malignancies such as breast, colon and renal cancers. These drugs target tumour cells and/or the microenvironment by exploiting specific molecular abnormalities in the tumour. This approach holds the promise of greater selectivity and lower toxicity than chemotherapy. Advances in our understanding of the biology of ovarian cancer has led to clinical trials of targeted agents in ovarian cancer. Of these approaches, angiogenesis inhibitors and poly(ADP-ribose)polymerase (PARP) inhibitors are the most developed[18].

Angiogenesis inhibitors

Angiogenesis, the formation of new blood vessels, is important for cancer growth and metastasis. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF-A), has shown significant single agent activity on ovarian carcinoma in phase II studies[19,20].

Two randomized trials, the Gynaecologic Oncology Group (GOG) trial 218 and International Collaborative Ovarian Neoplasm (ICON) 7 trials, both reported a progression-free survival advantage for the addition of bevacizumab to carboplatin/paclitaxel with subsequent maintenance bevacizumab as front-line therapy[21,22]. The benefit of bevacizumab is greater in patients defined as at the highest risk of progression (around 3.6 months). Furthermore, in ICON7, a significant improvement in overall survival with bevacizumab was seen in the high-risk group. The demonstration of a survival benefit of almost 8 months in patients with a poor prognosis is very encouraging. In addition, the OCEANS trial in which patients with recurrent platinum-sensitive disease were treated with bevacizumab in combination with chemotherapy (carboplatin with gemcitabine), has also shown a significant improvement in progression-free survival[23]. In the first-line trials, bevacizumab was stopped after a finite period of time and an important question that remains to be answered is whether or not a better outcome might be derived if bevacizumab is maintained until progression. Moreover, preclinical studies have suggested that release of VEGF inhibition may allow the regrowth of abnormal tumour[24]. Other VEGF targeting agents that have entered clinical trials in ovarian cancer include cedirinib sunitinib and sorafenib.

PARP inhibitors

Patients with BRCA mutations are at risk of developing ovarian cancer (10–40%). PARP inhibitors work by generating specific DNA lesions that require functional BRCA1 and BRCA2 for DNA repair. A phase II study of the PARP inhibitor, olaparib, demonstrated low toxicities and encouraging radiological and serological clinical responses (57.6% RECIST and CA-125 criteria)[25]. The promising activity of PARP inhibitors may not be limited to tumours harbouring germline BRCA mutations. Up to 50% of high-grade serous sporadic ovarian cancers may have defects (including somatic BRCA mutations, BRCA methylation) that confer sensitivity to PARP inhibition (BRCAness)[26]. A randomized trial has shown that maintenance therapy with PARP inhibitors extended progression-free survival by almost 4 months in patients with high-grade serous ovarian cancer with or without BRCA1 or BRCA2 germline mutations[27].

Other targeted agents

Examples of other signaling inhibitors in clinical trials include inhibitors of the PI3 kinase/AKT pathway, Src inhibitors and EGFR/HER2 inhibitors. The folate

receptor is overexpressed in >90% of ovarian cancers. Monoclonal antibodies to the alpha folate receptor are currently undergoing randomized trials and early data suggest that such an approach is active in ovarian cancer.

Conclusion

The systemic treatment of ovarian cancer remains a challenge. Issues include the identification of biomarkers to guide management and assess response, overcoming drug resistance and patient selection. An improved understanding of the molecular abnormalities involved in ovarian cancer and clinical trials with translational end points are critical to the development of candidate agents and for improving clinical outcome.

A major strategic goal is how to keep patients in remission after initial chemotherapy. The discovery of molecular markers that can select patients for their own individualized maintenance therapy would be a major advance.

Conflict of interest

The authors have no conflicts of interest to declare.

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