Recent advances in systemic treatments for ovarian cancer

Susana Banerjee, Martin Gore

The Royal Marsden NHS Foundation Trust, Gynaecology Unit, London, UK

Corresponding address: Prof Martin Gore FRCP PhD, The Royal Marsden Hospital, Fulham Road, London, SW3 6JJ, UK. Email: martin.gore@rmh.nhs.uk

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 1c; 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. 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. 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 for platinum in combination with paclitaxel and one showed no such benefit. 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/m²) 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. 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. 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. 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. 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. 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. 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. 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. 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. 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.
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 chemotherapy-sensitive 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 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.

**References**

[1] CRUK. Cancer Research UK ovarian incidence statistics. [http://infocancerresearchuk.org/cancerstats/types/ovary/incidence/](http://infocancerresearchuk.org/cancerstats/types/ovary/incidence/).

[2] Trimbos JB, Parmar M, Vergote I, et al. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. J Natl Cancer Inst 2003; 95: 105–112. PMid:12529343.

[3] Hoskins PJ, Le N, Gilks B, et al. Low-stage ovarian clear cell carcinoma: population-based outcomes in British Columbia, Canada, with evidence for a survival benefit as a result of irradiation. J Clin Oncol 2012; 30: 1656–1662. doi:10.1200/JCO.2011.40.1646. PMid:22493415.

[4] Bell J, Brady MF, Young RC, et al. Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2006; 102: 432–439. doi:10.1016/j.ygyno.2006.06.013. PMid:16860852.

[5] McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996; 334; 1–6. doi:10.1056/NEJM199601043430101. PMid:7494563.

[6] Piccart MJ, Bertelsen K, James K, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst 2000; 92: 699–708. doi:10.1093/jnci/92.9.699. PMid:10793106.

[7] Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. Lancet 2002; 360: 505–515. doi:10.1016/S0140-6736(02)09781-6. PMid:12241653.

[8] Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009; 374: 1331–1338. doi:10.1016/S0140-6736(09)61157-0. PMid:19767092.

[9] Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwest Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 2001; 19: 1001–1007. PMid:11181662.

[10] Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006; 354: 34–43. doi:10.1056/NEJMoai052985. PMid:16394300.

[11] Rustin GF, van der Burg ME, Griffin CL, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/ EORTC 55955): a randomised trial. Lancet 2010; 376: 1155–1163. doi:10.1016/S0140-6736(10)61268-8. PMid:20888983.

[12] Markman M, Markman J, Webster K, et al. Duration of response to second-line, platinum-based chemotherapy for ovarian cancer: implications for patient management and clinical trial design. J Clin Oncol 2004; 22: 3120–3125. doi:10.1200/JCO.2004.05.195. PMid:15284263.

[13] Parmar MK, Ledermann JA, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet 2003; 361: 2099–2106. PMid:12826431.

[14] Alberts DS, Liu PY, Wilczynski SP, et al. Randomized trial of pegylated liposomal doxorubicin (PLD) plus carboplatin versus carboplatin in platinum-sensitive (PS) patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy (Southwest Oncology Group Protocol S0200). Gynecol Oncol 2008; 108: 90–94. doi:10.1016/j.jygyno.2007.08.075. PMid:17949799.

[15] Pfisterer J, Flante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 2006; 24: 4699–4707. doi:10.1200/JCO.2006.06.0913. PMid:16966687.

[16] Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol 2010; 28: 3323–3329. doi:10.1200/JCO.2009.25.7519. PMid:20498395.

[17] Bookman MA, Brady MF, McGuire WP, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Oncology Intergroup. J Clin Oncol 2009; 27: 1419–1425. doi:10.1200/JCO.2008.19.1684. PMid:19224846.

[18] Banerjee S, Gore M. The future of targeted therapies in ovarian cancer. Oncologist 2009; 14: 706–716. doi:10.1634/theoncol.2009-0013. PMid:19592450.

[19] Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007; 25: 5156–511. doi:10.1200/JCO.2007.11.5345. PMid:17088993.

[20] Cappuzzo F, Sirtoli S, Craxi A, et al. Randomized controlled trial of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 2007; 25: 5180–5186. doi:10.1200/JCO.2007.12.0782. PMid:18024865.

[21] Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011; 365: 2473–2483. doi:10.1056/NEJMoai104390. PMid:22204724.
[22] Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011; 365: 2484–2496. doi:10.1056/NEJMoa1103799. PMid:22204725.

[23] Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012; 30: 2039–2045. doi:10.1200/JCO.2012.42.0505. PMid:22529265.

[24] Ebos JM, Lee CR, Cruz-Munoz W, Bjarnason GA, Christensen JG, Kerbel RS. Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. Cancer Cell 2009; 15: 232–239. doi:10.1016/j.ccr.2009.01.021. PMid:19249681.

[25] Audeh MW, Carmichael J, Penson RT, et al. Oral poly (ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet 2010; 376: 245–251. doi:10.1016/S0140-6736(10)60893-8. PMid:20609468.

[26] Banerjee S, Kaye SB, Ashworth A. Making the best of PARP inhibitors in ovarian cancer. Nat Rev Clin Oncol 2010; 7: 508–519. doi:10.1038/nrclinonc.2010.116. PMid:20700108.

[27] Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012; 366: 1382–1392. doi:10.1056/NEJMoa1105535. PMid:22452356.