symposium article

Optimal first-line treatment in ovarian cancer

F. A Raja¹, N. Chopra² & J. A. Ledermann¹*  
¹UCL Cancer Institute, Cancer Research UK and UCL Cancer Trials Centre, London, UK; ²UCL Hospitals, London, UK

Treatment of ovarian cancer remains challenging despite the high complete response rate seen after maximal surgical debulking surgery and platinum-combination chemotherapy. As most patients will relapse and eventually succumb to ovarian cancer, new strategies are urgently required to improve survival. A platinum–taxane combination has been the cornerstone of treatment for >15 years. Better use of these drugs is being explored through scheduling studies, and dose-dense or intraperitoneal (IP) therapies. Further improvements in treatment will most likely come from the integration of optimal chemotherapy with one or more of the hundreds of molecular-targeted agents that could be active in ovarian cancer. The greatest experience has been with anti-angiogenic agents. Two large phase III trials in first-line ovarian cancer have demonstrated a positive effect of bevacizumab when administered concurrently with chemotherapy and then as a maintenance treatment. In this review, we discuss the existing treatments for ovarian cancer and highlight areas of recent progress.

Key words: anti-angiogenic agents, dose-dense, first-line treatment, intraperitoneal chemotherapy, ovarian cancer

introduction

Ovarian cancer is the leading cause of death from gynaecological malignancies with an estimated 65,697 new cases and 41,448 deaths each year in Europe [1]. Approximately 15% of women present with disease localized to the ovaries and in this group with full staging surgery the 5-year survival is >90%. However, the majority of women present with advanced disease (International Federation of Gynaecological Oncology [FIGO] stage III–IV) and their survival at 5 years is poor, currently <30%. Early diagnosis is fundamental to achieving a high cure rate, but this is difficult due to the paucity of clearly defined symptoms. At present, there is no evidence for screening asymptomatic women although trials are in progress. There have been two large population-based screening trials. One from the USA was negative [2] and the other, UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), will report in 2 years.

Advanced ovarian cancer is most commonly diagnosed following presentation with symptoms and some of these may be present in early-stage disease. Goff et al. [3] reported that 89% of women with stage I/II disease had symptoms before diagnosis. As a result research is taking place to define ovarian cancer symptom indices to encourage earlier diagnosis through education of women and health care professionals [4, 5]. However it remains unclear whether these approaches to bring forward the diagnosis by a few months will identify disease at an earlier stage [6]. These temporal measures may be less important than understanding the underlying biology of ovarian cancer; identification of premalignant markers or molecular signatures may be a more fruitful approach.

In this review we will focus on improvements in current therapies based on surgery and systemic treatment. These have led to guidelines for optimal care [7, 8] that will continue to be modified as the results of research and new clinical trials emerge. We review here the optimal first-line management of early and advanced disease, the results of recently conducted trials and the possible changes in care that may occur from the results of studies currently underway with different chemotherapy schedules, route of administration and incorporation of molecularly targeted therapies.

early ovarian cancer

Most women with early ovarian cancer are cured by surgery. With adequate staging survival of patients with ‘low risk’ earlier stage disease is >90% without adjuvant chemotherapy [9]. Patients with FIGO Ic are at higher risk, as are patients with high grade disease and these patients are offered adjuvant chemotherapy [10]. The benefit of adjuvant chemotherapy was first clearly shown in two randomized trials, International Collaboration for Ovarian Neoplasia (ICON) 1 and the EORTC ACTION (Adjuvant Chemotherapy in Ovarian Neoplasm) trial that enrolled over 900 patients and reported as two separate trials and as a combined analysis [11–13]. There was a significant improvement in recurrence-free survival (76% versus 65% \( P = 0.001 \)) and overall survival (OS) in favour of chemotherapy (82% versus 74% \( P = 0.008 \)) at 5 years. This benefit has been maintained with further follow-up; the 10 year recurrence-free survival of patients in the ICON 1 study remains significant (HR = 0.70; \( P = 0.023 \)) [14]. At the time of these two adjuvant studies surgical staging was not always
optimal and the greatest effect of adjuvant chemotherapy in patients on the ACTION trial was seen in patients who had suboptimal surgery. Debate continues about the choice of chemotherapy, carboplatin alone or in combination with paclitaxel (Taxol, Generic off patent). Six cycles of carboplatin are usually given, but the GOG 157 randomized study showed that three cycles of carboplatin and paclitaxel were equivalent to six cycles [15]. All these studies underlined the vital importance of performing complete surgical staging and thorough pathological analysis. In one study, the specialty of the operating surgery was found to be the only independent prognostic variable [16]. With the confidence of adequate surgical staging most patients with Grade 1 or 2 disease, FIGO Ia or Ib would not be given adjuvant chemotherapy. However, it is recognized that histological subtype is also a prognostic factor for both early and late-stage disease, and that this should be taken into account when making treatment choices.

**clear cell and mucinous ovarian cancers**

The majority of patients are diagnosed with serous carcinomas (80–85%) and these tumours have a high response rate to platinum-based chemotherapy. Endometrioid carcinoma is the next most common subtype and the two least common are clear cell and mucinous carcinomas. It is now becoming clear that the pathogenesis of these, as well as low grade serous cancer may be distinct from high grade serous cancer. These tumours may be classified as type I ovarian cancers, whilst the type II tumours comprise the more common high grade serous carcinomas [17]. Both clear cell and mucinous tumours present more frequently at an earlier stage than serous cancers, and in this situation their prognosis is good, perhaps even better than stage I high grade serous cancer. Overall patients with type I ovarian cancer fare better following surgery [18]. Adjuvant chemotherapy is usually not given for stage I mucinous tumours. For clear cell cancers, the situation is less certain but stage IC cancers have a poorer prognosis and are generally treated as though the patient has advanced disease. The exception is perhaps IC due to intraoperative capsule rupture, where the prognosis is no worse than stage IA [19].

The prognosis of advanced stage mucinous [20] and clear cell cancers [21] is much worse than serous carcinoma and as a result chemotherapy regimens are being developed specifically for these tumour types, recognizing that standard chemotherapy is less good [22]. A Japanese led randomized trial under the auspices of the GCIG (Gynecologic Cancer Inter Group) has just been completed comparing carboplatin and paclitaxel with cisplatin and irinotecan. Standard chemotherapy is less good [22]. A Japanese led randomized trial under the auspices of the GCIG (Gynecologic Cancer Inter Group) has just been completed comparing carboplatin and paclitaxel with cisplatin and irinotecan. Standard chemotherapy, carboplatin alone or in combination with paclitaxel, with or without bevacizumab (mEOC/GOG241; NCT01081262).

Trials in uncommon tumour sub-types are challenging and require substantial international collaboration. Without such trials, progress in the treatment of patients with rarer tumours will be slow; these patients will continue to have a poorer prognosis. The GCIG has resolved to tackle this issue by making trials in uncommon gynaecological tumours a priority.

**advanced ovarian cancer**

Platinum-based drugs have been used to treat ovarian cancer since the late 1970s and cisplatin followed by carboplatin-based combinations has been the standard of care for >15 years. The combination of cisplatin with paclitaxel was shown to be superior to cisplatin and cyclophosphamide (GOG 111) [24] and by 2003, it was clear that carboplatin and paclitaxel were equivalent to cisplatin and paclitaxel [25, 26]. A similar benefit in overall survival of 11% was seen in the long-term follow up (median 6.5 years) of a European-Canadian Intergroup study using cisplatin-paclitaxel and GOG111 [27]. However the largest single trial, ICON 3 in which carboplatin and paclitaxel were compared with carboplatin or, cyclophosphamide, doxorubicin (Adriamycin, Generic off patent) and cisplatin (CAP) showed no advantage of adding paclitaxel [28].

Carboplatin and paclitaxel have become the ‘backbone’ of treatment of advanced ovarian cancer.

Over the last 15 years, a large number of randomized trials comprising >11 000 patients have been done which have added a third drug in combination, or in sequence without leading to any substantial increase in OS. GOG 182 (ICONS5) was the largest single chemotherapy trial done in advanced ovarian cancer, adding topotecan, gemcitabine or pegylated liposomal doxorubicin (PLD) as the third agent [29]. If docetaxel (Taxotere, Sanofi-Aventis) is substituted for paclitaxel, the toxicity profile is a little different; less neurotoxicity occurs but there is more myelosuppression and the PFS and OS have been shown to be similar [30].

**surgery in advanced ovarian cancer**

Ovarian cancer surgery is unique amongst solid tumours as it is carried out even when patients have widely disseminated and advanced disease. The standard of care for patients with advanced ovarian cancer consists of primary maximal debulking surgery and platinum-based chemotherapy. This forms the cornerstone of ovarian cancer treatment although almost all the data have been from retrospective trials and there has never been a randomized, controlled trial, demonstrating a survival benefit for upfront surgery. However, there is evidence that patients who undergo surgery carried out by a specialist in gynaecological cancer surgery have a better survival [31–33]. It is also clear that the amount of residual disease remaining after surgery is an important prognostic variable [34, 35] and together these factors very much support the role of primary surgery with maximal debulking of tumour. There is now consensus that ‘optimal debulking’ should refer to surgical resection without any macroscopic residual disease rather than <1 cm residual disease as previously accepted. [36]

Perhaps, the best evidence for the role of surgery comes from a study carried out by the EORTC in which patients with suboptimal primary surgery were randomly assigned to interval secondary debulking surgery during chemotherapy or no further surgery. The median survival was extended by 6
months from 20 to 26 months in this relative poor prognostic group and there was a 10% increase in the 2-year survival for patients undergoing second surgery, from 46% to 56% [37]. In some patients, it is very difficult to achieve maximal debulking at initial diagnosis because of the extent of disease, and because of this and the wish to avoid two operations the EORTC undertook a randomized trial of primary (neoadjuvant) chemotherapy versus primary surgery in a group of women who were considered eligible for resection at diagnosis. This EORTC-NCIC trial showed no detriment to group of women who were considered eligible for resection at initial diagnosis because of the extent of disease, and venous complications were higher in the primary debulking group compared with the interval debulking group. A similar trial has been conducted in the UK (MRC CHORUS) and it is anticipated that results will be available in 2013. The results of this trial will be combined with the EORTC-NCIC study providing a large randomized dataset. Debates on the merits of primary versus delayed surgery continue [39, 40], but there is now an increasing proportion of patients receiving primary chemotherapy to avoid the need for two operations and to provide an environment for achieving maximal cytoreduction at the time of surgery. This approach is also increasingly being applied to patients who present with stage IV disease. In this group maximal cytoreduction and survival appear better in women receiving primary chemotherapy followed by surgery [41]. As neoadjuvant chemotherapy becomes an established practice of care in some patients, it is important that clinical trials of new therapies acknowledge this pathway of care in the design.

dose intensity therapy and dose scheduling

dose intense chemotherapy

There have been three large phase III trials comparing intraperitoneal (IP) chemotherapy with IV chemotherapy. In the first study, 654 patients were randomly assigned to receive six cycles of IV cyclophosphamide in combination with either IV or IP cisplatin. The median survival was significantly longer in the IP arm (49 versus 41 months; $P = 0.02, HR 0.76$) [45]. The clinical relevance of this trial is now questionable as it was carried out before the introduction of taxanes. It did, however, form the basis for further trials of IP chemotherapy.

The second study, GOG 114, incorporated IV paclitaxel in each arm. Patients were randomly assigned to receive either IV paclitaxel 135 mg/m² over 24 h followed by IV cisplatin 75 mg/m² every 3 weeks for six courses or IV carboplatin (area under the curve 9) every 28 days for two courses, then IV paclitaxel 135 mg/m² over 24 h followed by intraperitoneal cisplatin 100 mg/m² every 3 weeks for six courses. In the 462 assessable patients, a substantial improvement in PFS was observed but the difference in OS was of borderline significance ($P = 0.05$). Again toxic effects were substantially higher in the experimental arm and 18% of patients received <2 courses of IP treatment [46].

A third trial, GOG 172, randomized 415 patients with residual disease ≤1 cm to receive IV paclitaxel and cisplatin or IV paclitaxel followed by IP cisplatin (day 1) and paclitaxel (day 8) [47]. A significant improvement in OS was demonstrated: 65.6 months in the IP arm compared with 49.7 months in the IV arm ($P = 0.03$). This was despite only 42% of patients completing six cycles of IP chemotherapy. Grade 3/4 toxicity was significantly greater and quality of life scores significantly worse in the IP arm.

The three trials described above all recorded favourable PFS or OS results for the IP arms. Nevertheless, the place of IP chemotherapy continues to generate controversy and has not been incorporated into standard treatment in spite of the NCI issuing a clinical alert in 2006 stating that patients with optimally debulked ovarian cancer should be considered for IP treatment. Issues of excess toxicity, lack of familiarity with placement and use of peritoneal catheters and concern over the design of trials have hindered its widespread use. In addition, some have attributed the observed survival benefit in GOG 172 to a ‘dose-dense’ approach of scheduling paclitaxel rather than IP administration of drugs. To resolve these issues and answer these questions phase II/III trials of IP versus IV chemotherapy are in progress in the USA, Japan, Canada and Europe. These all use carboplatin and paclitaxel as the control arms. The design of three ongoing studies is shown in Figure 1.

dose scheduling-dose-dense chemotherapy

Reducing intervals between chemotherapy cycles is a strategy that has been considered to improve the activity of drugs used to treat ovarian cancer. Dose-dense scheduling, reducing the time for tumour regrowth between cycles, has a good scientific rationale and in gynaecological cancers the concept has been stimulated by the results of a randomized study in Japan (JGOG 3016) in which carboplatin (AUC 6) and paclitaxel (180 mg/m²) were compared with thrice weekly carboplatin and weekly paclitaxel (80 mg/m²). A total of 637 patients with FIGO stage II–IV epithelial ovarian cancer were randomly
assigned and after a median follow-up of 29 months, the median PFS was 17.2 months in the standard thrice weekly arm compared with 28 months in the dose-dense arm (HR 0.71; 95% CI 0.58–0.88). The 3-year OS (median follow-up 42 months) was also substantially higher in the dose-dense arm (65.1% versus 72.1%; HR 0.75; 95% CI 0.57–0.98) [48]. This improvement in survival is the largest benefit seen for many years in any phase III trial in ovarian cancer. This was despite the high dropout rate in the dose-dense arm with only 61% receiving six cycles of chemotherapy compared with 73% in the standard arm. The considerable excitement generated by this study is slightly tempered by the fact that the study was almost exclusively carried out in Asian patients. There is some evidence of ethnic differences in the expression of alleles involved in chemotherapy drug metabolism [49]. Therefore, it is unclear whether the magnitude of benefit observed in the Japanese study will be seen in Caucasian populations. There are a number of international trials in progress to assess dose-dense regimens further and determine applicability worldwide.

The Italian trial, MITO 7 (Figure 2A), is comparing thrice weekly carboplatin (AUC 6) and paclitaxel (175 mg/m²) with weekly carboplatin (AUC 2) plus weekly paclitaxel (80 mg/m²) (NCT00660842). The NCRI-led ICON8 study is a pragmatic three arm first-line study for all but low risk stage I ovarian cancer patients. It is designed to investigate dose fractionation

**Figure 1.** Ongoing trials in intraperitoneal (IP) and dose-dense chemotherapy. FT, fallopian tube; PPC, primary peritoneal cancer.
Figure 2. (A) Phase III Mito 7 trial: weekly carboplatin and paclitaxel. (B) Phase III ICON8 trial: weekly paclitaxel and carboplatin. (C) Phase III GOG 262 trial: weekly paclitaxel and optional bevacizumab. Neoadjuvant chemotherapy and interval debulking surgery also permitted in the study.
of both carboplatin and paclitaxel and is also the first trial to have a pre-specified stratification allowing immediate or delayed primary surgery. (Figure 2B)

It is postulated that the benefit seen with dose-dense paclitaxel may be due to an anti-angiogenic and pro-apoptotic effect. There is good rationale therefore for combining a weekly paclitaxel regimen with an anti-angiogenic agent such as bevacizumab. GOG 262 is evaluating weekly paclitaxel plus thrice weekly carboplatin compared with standard thrice weekly carboplatin and paclitaxel in stage II–IV ovarian cancer. (NCT01167712). Additional concurrent and maintenance bevacizumab is an option in this trial. The disadvantage of this approach is that a benefit of dose-dense chemotherapy may not be separable from the benefit of maintenance bevacizumab. See Figure 2C.

If the above trials confirm the results of JGOG 3016, then it is highly likely that dose-dense chemotherapy will become an internationally accepted standard of care.

**molecular-targeted therapies**

As a result of a greater understanding of the molecular pathways involved in carcinogenesis and tumour growth, a large number of potential therapeutic targets have been identified and drugs to block receptors, ligands or pathways are being developed. Many are in the early stages of development, particularly in patients with recurrent disease, whilst other drugs have been examined in first-line therapy of ovarian cancer in large phase III trials. Bevacizumab, a monoclonal antibody directed against the vascular endothelial growth factor (VEGF), is the most thoroughly investigated agent and has shown great promise in ovarian cancer (see table 1).

**anti-angiogenic agents**

Two first-line trials have been completed and published (See Figure 3). The GOG 218 trial investigated the addition of bevacizumab (15 mg/kg) every three weeks to standard three weekly carboplatin plus paclitaxel in a randomized, double-blinded, three arm placebo controlled study. Overall, the trial enrolled 1873 patients with stage III–IV ovarian cancer who had residual disease after primary debulking surgery. In the two experimental arms, bevacizumab was given with chemotherapy and then continued as maintenance for a further 16 cycles (total duration 15 months) in one arm, whilst in the other arm patients switched to placebo after chemotherapy. PFS was the primary end-point and a substantial benefit was seen in the bevacizumab maintenance arm compared with the control arm (10.3 versus 14.1 months, HR 0.717; 95% CI 0.625–0.824; P < 0.001). No benefit was seen when bevacizumab was given only with chemotherapy (10.3 versus 11.2 months, HR 0.908; 95% CI 0.795–1.040, P = 0.16). No difference in OS was observed among the three arms at the time of the PFS analysis [50]. A second open label phase III trial (ICON7) in 1528 high-risk early-stage or advanced ovarian cancer patients examined the addition of thrice weekly bevacizumab (7.5 mg/kg) concurrent to standard carboplatin and paclitaxel followed by maintenance bevacizumab for 12 cycles or until disease progression [51]. The majority (70%) of patients had stage IIIC–IV ovarian cancer. The PFS at 36 months was substantially greater in patients receiving bevacizumab (21.8 versus 20.3; HR 0.81; 95% CI 0.70–0.94; P = 0.004). An updated analysis of high-risk patients (30%) (stage IV or stage III with >1 cm residual disease) at 42 months, demonstrated a greater magnitude of benefit: 14.5 months for standard therapy versus 18.1 months with bevacizumab added. In both the trials, the addition of bevacizumab was well-tolerated. Hypertension was not a significant problem with ≥grade 2 toxicity observed in 18% of patients in the bevacizumab arm (<1% in the control arm) in ICON7. In the GOG 218 study, grade ≥2 hypertension was observed in 16.5 and 22.9% in the two bevacizumab arms compared with 7.2% in the control arm. The incidence of other toxic effects such as gastrointestinal perforation and proteinuria were uncommon in both the trials.

The results of ICON7 are intriguing for a number of reasons. First, the dose used is half that of the dose in GOG218 and the duration of therapy is shorter (12 versus 16 cycles). Second, the maximum benefit of bevacizumab was seen at 12 months (around the time of bevacizumab completion) and had disappeared by 24 months. It may be that the optimal administration of bevacizumab is until progression as occurred in the OCEANS study in recurrent ovarian cancer where a greater magnitude of benefit of bevacizumab was observed [52]. There are pre-clinical data to support this where the lifting of VEGF inhibition resulted in a more malignant phenotype of tumours. The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) group is developing a trial in first-line therapy to examine an extended duration of therapy with bevacizumab (15 months versus 30 months) (ENGOT-ov15/AGO-OVAR 17).

These landmark trials have raised many questions regarding dose, schedule and patient selection. Bevacizumab was approved by the European Medicines agency in December 2011 for use in ovarian cancer although the considerable cost is likely to pose a major hurdle for many countries. The fourth Ovarian Cancer Consensus meeting of the GCIG concluded that bevacizumab could be incorporated as a control arm of future studies [53].

**other anti-angiogenic drugs**

Oral inhibitors of the VEGF receptor (VEGFR) tyrosine kinase have been shown to have activity in patients with recurrent ovarian cancer, resulting in tumour responses and stabilization of disease, delaying tumour progression [54–58]. Two agents are now in first-line studies. Pazopanib is an angiogenic inhibitor with broad spectrum activity against all three VEGF receptors, platelet derived growth factor receptor (PDGFR) and c-Kit that has been approved for use in first-line advanced renal cancer. Over 900 patients including a sub-set in Asia have been recruited to a maintenance study, in which patients receive pazopanib 800 mg daily or placebo until progression, or up to 2 years (AGO OVAR-16; NCT 00866697; 01227928). The primary end-point is PFS.

The second trial is with nintedanib (BIBF1120), a potent inhibitor of VEGFR/PDGFR and fibroblast growth factor receptor. In this trial, nintedanib or placebo is given with a
standard regimen of carboplatin and paclitaxel after surgery and continued as maintenance therapy for up to 2 years (AGO OVAR-12 trial NCT01015118). This trial also has PFS as its primary end-point.

The incidence of hypertension in these oral multikinase anti-angiogenic agents is higher than bevacizumab. Side-effects reported previously in trials of pazopanib in recurrent disease include fatigue, diarrhoea and nausea [54]. Less hypertension has been reported with nintedanib but nausea, diarrhoea and abnormal liver function were the most frequently described side-effects using 250 mg bd [55]. The dose in the first-line study is 200 mg.

Targeting the angiopoietin axis is another strategy to develop anti-angiogenic therapy. AMG 386, a peptibody inhibiting the interaction of angiopoietin-1 and -2 to the Tie2 receptor, has been evaluated in combination with weekly paclitaxel in recurrent ovarian cancer [59]. The results of a phase II trial have been promising and have led to further exploration within the TRINOVA-3 trial of AMG 386/placebo plus carboplatin/paclitaxel in first-line ovarian cancer (NCT00866997 (OVAR16)).

EGFR

The epidermal growth factor receptor (EGFR) is overexpressed in up to 70% of ovarian cancer patients [60]. However, responses to EGFR inhibitors in recurrent ovarian cancer are infrequent, and as with lung cancer are dependent on the presence of a mutation in the catalytic domain of the EGFR [61]. Erlotinib is a highly potent oral inhibitor of the tyrosine kinase region of the EGFR and this has been studied in an EORTC trial in which patients with high-risk stage I and stage II-IV epithelial ovarian cancer who had completed platinum-based chemotherapy were randomly assigned to erlotinib maintenance therapy or observation following chemotherapy. The trial completed recruitment in 2008 and the results are due to be presented this year.

IGFR inhibitors

Insulin growth factor 1(IGF 1) is involved in the inhibition of apoptosis, tumour progression and metastases. AMG 479 is a monoclonal antibody that is a potent inhibitor of the IGF 1 receptor and OSI-906 is an oral dual kinase inhibitor of IGFR1 and the insulin receptor. The latter is in clinical trials in recurrent ovarian cancer. The results of the trials with the former are not available but a randomized phase II study of AMG 479 added to first-line chemotherapy in patients with optimally debulked ovarian cancer is underway. (NCT00718523)

**biomarkers for selection of treatment**

Positive results of molecular-targeted therapy are beginning to emerge but studies thus far in first-line therapy have been in unselected women with ovarian cancer. The identification of predictive biomarkers in ovarian cancer has been challenging. Two markers are currently being investigated in recurrent ovarian cancer. The first is a mutation of the BRCA gene. This is a marker for deficiency of DNA repair through the homologous recombination pathway. BRCA tumours are

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### Table 1. First-line trials in ovarian cancer with targeted agents

<table>
<thead>
<tr>
<th>Target Agent</th>
<th>Chemotherapy</th>
<th>RCT</th>
<th>Placebo</th>
<th>C. M</th>
<th>Size</th>
<th>End-point</th>
<th>Trial number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular endothelial growth factor (VEGF)</td>
<td>Bevacizumab platinum-taxane</td>
<td>III</td>
<td>N</td>
<td>C + M</td>
<td>1500</td>
<td>PFS</td>
<td>NCT00483782 *(ICON7)</td>
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<tr>
<td>VEGF</td>
<td>Bevacizumab platinum-taxane</td>
<td>III</td>
<td>Y</td>
<td>C + M</td>
<td>2000</td>
<td>PFS</td>
<td>NCT00262847 *(GOG 218)</td>
</tr>
<tr>
<td>Epidermal growth factor receptor (EGFR) TKI</td>
<td>Erlotinib platinum-based</td>
<td>III</td>
<td>Y</td>
<td>M</td>
<td>800</td>
<td>PFS</td>
<td>NCT00263822 (EORTC 55041/MRC OVO7)</td>
</tr>
<tr>
<td>Vascular endothelial growth factor receptor (VEGFR)</td>
<td>Pazopanib platinum-based</td>
<td>III</td>
<td>Y</td>
<td>M</td>
<td>900</td>
<td>PFS</td>
<td>NCT00866997 (OVAR16)</td>
</tr>
<tr>
<td>VEGFR</td>
<td>Nintedanib (BIBF1120) platinum-taxane</td>
<td>III</td>
<td>Y</td>
<td>C</td>
<td>1300</td>
<td>PFS</td>
<td>NCT01015118</td>
</tr>
<tr>
<td>EGFR TKI</td>
<td>Erlotinib Bevacizumab platinum-taxane</td>
<td>LI</td>
<td>N</td>
<td>C + M</td>
<td>60</td>
<td>PFS</td>
<td>NCT00520013</td>
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<tr>
<td>VEGFR, PDGFR c-Kit</td>
<td>Sorafenib platinum-taxane</td>
<td>LI</td>
<td>N</td>
<td>C + M</td>
<td>60</td>
<td>PFS</td>
<td>NCT00390611</td>
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<td>Y</td>
<td>M</td>
<td>250</td>
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<tr>
<td>IGF R1</td>
<td>AMG 479 platinum-taxane</td>
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<td>Y</td>
<td>M</td>
<td>160</td>
<td>PFS</td>
<td>NCT00718523</td>
</tr>
</tbody>
</table>

C, combination; OS, overall survival; M, maintenance; PFS, progression-free survival; FGFR, fibroblast growth factor receptor.

*Published trials.*

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particularly susceptible to inhibitors of PARP (poly-ADP ribose polymerase) [62]. Clinical trials in recurrent ovarian cancer have demonstrated single-agent activity of olaparib, a PARP inhibitor in patients with BRCA mutations and recurrent ovarian cancer [63]. There is evidence that HR deficiency may be more prevalent in ovarian cancer, present in a substantial proportion of patients with high grade serous cancer. Responses to olaparib have been reported in BRCA negative patients, particularly those that have platinum-sensitive relapse [64]. A randomized maintenance trial of olaparib in patients with and without germ-line mutations has shown a substantial delay in time to progression of disease [65] and trials in first-line therapy are now being considered.

Folate receptor α is overexpressed in ovarian cancer and represents a target for therapy. Trials are underway with a monoclonal antibody, farletuzumab targeting the folate receptor [66] and if these prove positive it is likely that studies will be extended into first-line therapy. Similarly, selectively therapy targeting the folate receptor is being developed by using EC145, a conjugate of desacetylvinblastine monohydrazide (vintafolide) linked through a peptide spacer to the folate receptor targeting moiety. The first study, PRECEDENT comparing EC145 and PLD and PLD alone, showed an improvement in PFS [67]. This was most marked in patients whose tumours had high expression of folate receptor α demonstrated by Technetium-EC20 imaging. A phase III trial, PROCEED, is now being planned, and importantly patients will have imaging of tumours performed with Technetium-EC20 before randomization.

**conclusions**

The treatment of ovarian cancer remains challenging despite many advances in therapeutic options. There is still place for examining better ways of using known drugs and the results of ongoing trials over the next few years will further increase our knowledge about the optimum use of chemotherapy. Targeted agents are showing promise in many situations and have in general less toxicity than conventional chemotherapy. Molecular-targeted therapy is moving into earlier phases of
treatment but most are still being studied without prior knowledge of likely efficacy which is a wasteful use of expensive resources. There needs to be a greater focus on identifying predictive markers of response to these agents if we are to see their widespread use in clinical practice.

disclosure

The authors have declared no conflicts of interest.

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