TARGETED THERAPIES IN OVARIAN CANCER

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Abstract

Epithelial ovarian cancer is a challenging disease to treat, with the majority of patients presenting with advanced disease. Despite aggressive surgical debulking and platinum-based chemotherapy, many patients ultimately relapse and die of their disease. There is a real clinical need to improve outcomes in ovarian cancer. The last decade has seen the emergence of a number of targeted therapies that have been incorporated into the management of common malignancies such as breast, colon and lung cancer. Recently, Phase III trials of targeted therapies, including bevacizumab, cediranib and erlotinib, have commenced in ovarian cancer following encouraging Phase II results. The potential role of targeted therapies will be established in this disease over the coming years.

Ovarian cancer is the most common cause of death from gynaecological malignancies in Australia.[1] The majority of patients with epithelial ovarian cancer have advanced disease at presentation, with spread throughout the peritoneal cavity. Despite aggressive surgical debulking and platinum-based chemotherapy, the five year disease free survival rate is approximately 20-25% for these patients.[2-4] In an effort to improve outcomes several strategies have been tested.

The addition of a third non-cross resistant chemotherapy with either an anthracycline, gemcitabine or topotecan has not improved outcomes compared to standard treatment with carboplatin and paclitaxel.[5,6] Maintenance chemotherapy involves extending treatment, generally with a less intense regimen after a favourable response to chemotherapy. Although one trial (SWOG9701/GOG178) found an improved progression-free survival with paclitaxel given monthly for 12 months, compared with three months after standard chemotherapy, other maintenance/ consolidation trials failed to confirm this benefit.[7-10] Intensifying treatment with high-dose chemotherapy and peripheral stem cell support did not result in a progression-free or overall survival advantage compared with standard treatment.[11]

The preliminary results of the JCOG3016 trial were presented at the 2008 American Society of Clinical Oncology (ASCO) meeting. This compared standard chemotherapy with conventional dose carboplatin and paclitaxel versus carboplatin and weekly paclitaxel. There was a significant improvement in progression-free survival. Overall survival data is immature with median survival not yet reached in either arm.[12]

The three largest randomised Phase III trials of intraperitoneal chemotherapy for patients with optimally debulked disease have suggested an additional benefit for the inclusion of an intraperitoneal component of delivery.[4,13,14] One of the main concerns associated with intraperitoneal chemotherapy is the associated toxicity, with over half of patients unable to complete planned treatment. Based on current data, there is considerable controversy as to whether this should constitute standard therapy.[15] An intraperitoneal regimen with more acceptable toxicity profile is needed.

Recently there has been considerable interest in exploring targeted therapies in epithelial ovarian cancer. The most promising agents to emerge include the anti-angiogenic agents and Poly ADP-ribose polymerase (PARP) inhibitors. This review will focus on agents that have entered Phase II and III clinical trials (see tables 1 and 2).

Anti-angiogenic agents

Vascular endothelial growth factor (VEGF) has been shown to be associated with tumour progression and ascites formation in ovarian cancer. The majority of invasive ovarian cancers express VEGF.[36] Several studies have correlated high intratumoural microvascular density and elevated VEGF expression with poor prognosis in ovarian cancers.[37-40] In animal models, blocking VEGF has been found to inhibit ascites formation.[41] Thus there is a strong rationale for targeting VEGF and its receptors in ovarian cancer.

Bevacizumab

Bevacizumab is a humanised anti-VEGF monoclonal antibody. Two Phase II trials in recurrent epithelial ovarian cancer and primary peritoneal cancer have confirmed the single-agent activity of bevacizumab. The response rates seen compare favourably to other malignancies such as colon and breast cancer which have Therapeutic Goods Administration approval.

A study by the Gynecology Oncology Group (GOG170-D) treated 62 patients with bevacizumab 15mg/kg IV every three weeks. The majority of patients (66.1%) had received two prior chemotherapy regimens and 41.9% were platinum resistant. The overall response rate was 21% (including two patients with a complete response). The progression-free survival rate at six months was 40.3%.[16]

Cannistra and colleagues also used this schedule.[17] They treated 44 patients, all of whom were platinum-resistant. Additionally, all patients had progressed during or within three months of receiving either topotecan or liposomal doxorubicin. Patients were heavily pre-treated, with 47.7% having received three prior chemotherapy regimens. This trial initially planned to enrol 120 patients, but was discontinued early due to safety concerns, with 11.4% of patients experiencing

Table 1: *Adjuvant trastruzumab trials in operable breast cancer.*

Study	N	Schedule	Patient population	Response
Bevacizumab				
Burger MA et al.[16] (2007)	62	15 mg/kg every 3 weeks	Platinum sensitive and resistant. 1-2 prior chemotherapy lines.	21%
Cannistra SA et al.[17] (2007)	44	15 mg/kg every 3 weeks	Platinum resistant. Up to 3 prior chemotherapy lines.	15.9%
Aflibercept (AVE0005)				
Tew WP et al.[18] (2007)	162	2 mg/kg or 4 mg/kg every 2 weeks	Platinum resistant. Liposomal doxorubicin or topotecan resistant. 3-4 prior chemotherapy lines.	8% †
Cediranib (AZD2171)				
Hirte HW et al.[19] (2008)	60	45 mg daily (reduced to 30 mg)	Platinum sensitive and resistant. 1 prior chemotherapy.	NR †
Matulonis UA et al.[20] (2008)	29	45 mg daily (reduced to 30 mg)	Platinum sensitive and resistant. Up to 3 prior chemotherapy lines.	18.5% †
Sunitinib (SU11248)				
Biagi JJ et al.[21] (2008)	17	50 mg daily for 4 of 6 weeks	Platinum sensitive and resistant. 1-2 prior chemotherapy lines.	11.8% †
Sorafenib (BAY 43-9006)				
Matei D et al.[22] (2008)	73	400 mg bd daily	Platinum sensitive and resistant. 1-2 prior chemotherapy lines.	3.4% †
Pazopanib (GW786034)				
Friedlander M et al.[23] (2007)	17	800 mg daily	Platinum sensitive and resistant. 1-2 prior chemotherapy lines.	47% Ca125 response †
Erlotinib (OSI-774)				
Gordon AN et al.[24] (2005)	34	150 mg daily	EGFR +ve tumours.	6%
Gefitinib (ZD 1839)				
Posades EM et al.[25] (2007)	24	500 mg daily	No limit on prior chemotherapy.	0%
Schilder RJ et al.[26] (2005)	27	500 mg daily	Platinum sensitive and resistant. 1-2 prior chemotherapy lines.	4%
Cetuximab (C225)				
Schilder RJ et al.[27] (2007)	25	400 mg/m2 bolus then 250 mg/m2 for two 3 week cycles	EFGR +ve tumours. 1-2 prior chemotherapy lines.	4%
Matuzumab (EMD72000)				
Seiden MV et al.[28] (2007)	37	800 mg weekly	EFGR +ve tumours. No limit on prior chemotherapy.	0%
Pertuzumab (rhuMAb 2C4)				
Gordon MS et al.[29] (2006)	123	840 mg loading then 420 mg or 1050 mg every 3 weeks	28.6% HER2 +ve ELISA. Platinum sensitive and resistant. No limit on prior chemotherapy.	4.3%
Trastuzmab				
Bookman MA et al.[30] (2003)	41	4 mg/kg loading then 2 mg/kg weekly	HER 2 IHC 2+ or 3+. No limit on prior chemotherapy.	7.3%
Imatinib				
Posades EM et al.[31] (2007)	23	400 mg daily bd (reduced to 600mg daily)	Up to 4 prior chemotherapy lines.	0%
Alberts DS et al.[32] (2007)	19	400 mg daily	Expressed kit (CD117) or PDGFR. Platinum resistant. 1 prior line of chemotherapy.	0%
Coleman RL et al.[33] (2006)	16	600 mg daily	Over-expressed one of c-kit, PDGFR of c-Abl. Platinum resistant.	0%
Ovegovomab				
Ehlen TG et al.[34] (2005)	13	2 mg weeks 0,2,4,8,12 then 3 monthly	1 or more prior chemotherapy lines.	0%
CGP 69846A				
Oza AM et al.[35] (2003)	22	4mg/kg/day for 21 days every 28 days	1-2 prior chemotherapy lines.	0%

† Preliminary results reported only for patients evaluable for response.

gastrointestinal perforations. The overall response rate was 15.9%. A further 25% achieved stable disease for greater than three months. On review, all five patients with perforations had received three prior regimens and had radiological evidence of bowel involvement.[17]

Bevacizumab 10mg/kg every two weeks and cyclophosphamide 50mg daily were evaluated in 70 patients with recurrent epithelial ovarian cancer. Patients may have received up to three prior regimens and 60% were platinum-sensitive. The overall response rate was 24%. Progression-free survival at six months was 56%. The incidence of gastrointestinal perforation was 6%.[42]

Ongoing Phase II studies are investigating bevacizumab in combination with chemotherapy and other targeted agents. There are currently three large Phase III trials underway incorporating bevacizumab into first and second-line treatment: GOG 218, ICON 7 and GOG 213 (table 2). Each of these trials is studying bevacizumab in combination with chemotherapy, including carboplatin and a taxane followed by maintenance. If these trials are positive, the relative benefit of bevacizumab with chemotherapy, or as maintenance, will be difficult to separate. The GOG 218 trial has a third arm, which will provide some information on the relative benefit of the maintenance component of therapy.

Aflibercept (AVE0005) VEGF Trap

VEGF Trap is a fusion protein composed of the extracellular domains of human VEGFR1 (domain 2) and VEGFR2 (domain 3) fused to IgG1 Fc molecule. This binds to all VEGF-A isoforms and placental growth factor. This antibody binds VEGF with high affinity, interfering with binding and subsequent activation of native receptors.

The preliminary results of a double-blinded randomised Phase II trial evaluating aflibercept at 2mg/kg every two weeks, or 4mg/kg every two weeks in recurrent epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer, were presented at the 2007 ASCO meeting. Efficacy data was available on the 162 patients. All received three to four prior chemotherapy regimens and were platinum resistant. Additionally, patients had documented resistance to either liposomal doxorubicin or topotecan. The pooled blinded data demonstrated a response rate of 8% by Response Evaluation Criteria in Solid Tumours (RECIST) criteria and 13% with Ca125 declines. Forty-one per cent had maintained either partial response or stable disease at 14 weeks. Ascites was present at baseline in 23 patients, of whom 29% had complete disappearance of ascites and in a further 54% there was no increase. The most common toxicity was hypertension (18%, grade 3/4). Two patients have had bowel perforation.[18]

Phase II studies in ovarian cancer are ongoing, including one trial which is comparing aflibercept versus placebo in patients with recurrent symptomatic ascites.

Cediranib (AZD2171)

Cediranib is a highly potent inhibitor of VEGFR2, VEFGR1, VEGFR3, platelet derived growth factor receptor (PDGFR) and C-KIT. The preliminary Phase II results for two trials were presented at the 2008 ASCO meeting. Both trials are now closed to recruitment and final data is awaited. Patients included both platinum-sensitive and platinum-resistant. In both trials the initial dose of 45mg daily was subsequently reduced to 30mg daily due to cardiovascular toxicity and hypertension. The most common grade 3 or 4 toxicity included

Table 2: *Ongoing Phase III trials.*

Study	N	Patient population	Study Arms	Endpoint	Status
GOG 218	2000	First line Stage III and IV Sub-optimal debulking	I. Paclitaxel, carboplatin and placebo x 6 then placebo for up to 22 cycles. II. Paclitaxel, carboplatin and bevacizumab x 6 then placebo for up to 22 cycles. III. Paclitaxel, carboplatin and bevacizumab x 6 then bevacizumab for up to 22 cycles.	OS	Open
ICON 7	1520	First line High risk Stage I and II-IV	I. Paclitaxel and carboplatin x 6. II. Paclitaxel and carboplatin and bevacizumab x 6 then bevacizumab for up to 12 cycles.	PFS	Open
GOG 213	660	First relapse Platinum-sensitive Secondary cryoreduction	I. Paclitaxel (or docetaxel) and carboplatin x 6 – 8. II. Paclitaxel (or docetaxel) and carboplatin and bevacizumab x 6 - 8 then bevacizumab until PD.	OS	Open
ICON 6	2000	First relapse Platinum-sensitive	I. Paclitaxel, carboplatin and placebo (daily) x 6 then placebo (daily) for up to 18 months. II. Paclitaxel, carboplatin and cediranib (daily) x 6 then placebo (daily) for up to 18 months. III. Paclitaxel, carboplatin and cediranib (daily) x 6 then cediranib (daily) for up to 18 months.	OS	Stage I Open
EORTC 555041	830	Following first line platinum-based chemotherapy High risk Stage I and II-IV	I. Erlotinib (daily) for up to 2 years. II. Observation.	PFS	Closed to recruitment

OS Overall survival; PFS Progression-free survival

hypertension and fatigue. No bowel perforations have been seen in either study.[19,20]

ICON 6 is a placebo-controlled trial randomising patients with platinum-sensitive ovarian cancer at first relapse to one of three arms (table 2). This trial will be conducted in three stages and has opened with an interim safety analysis planned after the first 50 patients.

Other small molecule multi-targeted tyrosine kinase inhibitors

The preliminary Phase II results have been presented for three agents, sorafenib, sunitinib and pazopanib, as summarised in table 1. Each trial included patients with platinum-sensitive and platinum-resistant disease and one or two prior treatments were permitted. Activity for each of these agents appears promising, however it is too early for meaningful comparison between these agents or with the other VEGF inhibitors.[21-23] Ongoing Phase II trials are also investigating these agents in combination with chemotherapy.

Other drugs with anti-angiogenic activity that have entered Phase II clinical trials in ovarian cancer include: the multi-targeted tyrosine kinase inhibitors AMG 706, Vandetanib (ZD 6474), XL999 and BIBF1120; a VEGFR-2 inhibitor, CP-547632; and a protein kinase Cß inhibitor Enzastaurin (LY317615).

Poly ADP-ribose polymerase inhibitors

Germline mutations in BRCA1 and BRCA2 are associated with an increased risk of developing ovarian cancer. A Canadian study found BRCA mutations in 13.2% of 1171 unselected patents with an incident ovarian cancer diagnosis. For patients with serous pathology this increased to 18%.[43]

BRCA deficient cells are unable to repair endogenous DNA damage via homologous recombination and rely on base excision repair. PARP inhibitors inhibit base excision repair, thereby leaving BRCA1 and BRCA2 deficient cells susceptible to apoptosis from increased DNA damage.

AZD2281 (KU-0059436)

The first Phase I trial of this agent was reported at the 2007 ASCO meeting. Updated results for 50 patients with ovarian cancer and BRCA mutations were presented in 2008. This analysis included 11 patients in the dose escalation stage and 39 patients in the second expansion phase treated at 200 mg bd. Patients were platinum-sensitive (n=10), platinum-resistant (n=27) or platinum-refractory (n=13). The medium number of prior treatments was three (range 1-8). The combined results found a 28% response rate by RECIST criteria and 39% by GCIG Ca125 criteria. There were increased responses seen in the platinum sensitive group, however responses were seen across each category.[44]

Phase I and II trials are ongoing, including combining AZD2281 with chemotherapy. Two other PARP inhibitors, AG014699 and BSI-201, have recently commenced Phase II studies in patients with BRCA mutations and ovarian cancer.

Epidermal growth factor receptor inhibitors

Epidermal growth factor receptor (EGFR) over-expression has been documented in ovarian cancer, however there is wide variability in the frequency this is reported. Activating mutations of EGFR are rarely identified in ovarian cancer.[45,26]

Erlotinib and gefitinib are small molecular inhibitors of EGFR (HER 1). Small Phase II trials in patients with recurrent ovarian cancer have not documented significant activity.[24-26] One study with erlotinib in heavily pre-treated platinum-refractory patients, found that patients who developed a rash survived significantly longer than patients who did not.[24] Ongoing Phase II studies are combining these agents with chemotherapy and other target therapies.

EORTC 55041 is a randomised trial of maintenance erlotinib for up to two years versus observation in patients with high risk stage I and stage II-IV epithelial ovarian cancer, fallopian tube and primary peritoneal cancer, who either responded or had stable disease after first line platinum-based chemotherapy. This trial completed accrual in February 2008.

Cetuximab and matuzumab are humanised anti-EGFR (HER 1) monoclonal antibodies. Eligibility for these Phase II studies included EGFR-positive tumours. Each of these agents as monotherapy has failed to demonstrate significant activity.[27,28] Two Phase II trials of cetuximab with platinum-based chemotherapy have shown that although combination therapy is tolerable, compared to historical data there was no increase in progression-free survival.[46,47]

Human epidermal growth factor receptor 2 (HER2) inhibitors

Pertuzumab and trastuzumab are monoclonal antibodies that bind the HER2 preventing dimerisation with other HER molecules, thereby preventing activation and blocking downstream signals. In the trial of trastuzumab that included only patients with HER 2 positive tumours, of 837 patients screened, 11.5% were found to have HER 2+ and 3+ tumours as assessed by immunohistochemistry. Phase II trials have shown minimal activity.[29,30] Trials of pertuzumab with chemotherapy continue, with preliminary reports confirming such combinations are well tolerated.[48,49]

Several Phase II studies of the agent lapatinib, which is a dual inhibitor of EGFR and HER2, either as a single agent or in combination with chemotherapy are ongoing.

Platelet derived growth factor receptor inhibitors

Imatinib is an inhibitor of C-KIT and PDGFR. Three small phase II trials, two of which enrolled patients with documented over-expression of either C-KIT of PDGFR, did not demonstrate activity in patients with relapsed disease.[31-33]

Ca125

Oregovomab is a fully murine antibody specific for the Ca125 antigen. Two Phase II studies demonstrated that

patients who mounted an immune response after infusion of oregovomab, may experience prolonged disease stabilisation or an improved survival.[34,50]

A Phase III trial of oregovomab in patients with stage III/IV ovarian cancer, who have had a favourable response to chemotherapy, was presented at the 2008 ASCO meeting. Oregovomab was used as maintenance after chemotherapy with a 2:1 randomisation of oregovomab placebo (249:118). The primary endpoint was progression-free survival. There was no difference in progression-free survival between the two treatment arms. Patients who failed to mount an immune response had a worse prognosis.[51] Ongoing trials of this agent have been discontinued.

Folate receptor alpha inhibitor

Folate receptor alpha is over-expressed on the majority of patents with epithelial ovarian cancer.

MORAb-003 is a humanised monoclonal antibody against folate receptor alpha. An ongoing Phase II trial is evaluating the efficacy of MORAb-003 at first relapse with platinum sensitive ovarian cancer. Patients with symptomatic relapse also received concurrent chemotherapy with a platinum and taxane. The preliminary results from 52 patients have suggested activity with 100% normalisation of Ca125 in patients who received chemotherapy and three of eight patients with a second remission greater than the first.[52]

c-raf kinase inhibitor

One Phase II trial of a c-raf kinase inhibitor failed to demonstrate clinical activity.[35]

Other potential targets

There are a number of other targeted therapies that have commenced Phase II trials in ovarian cancer. These include: temsirolimus (CCI-779), a mammalian target of rapamycin (mTOR) inhibitor; ionafanib, a farnesyl transferase inhibitor; AZD6244, a mitogen-activated extracellular signal regulated protein kinase (MEK) inhibitor; AZD0530, dual inhibitor of SRC and ABL protein tyrosine kinases; and catumaxomab, an antibody to human CD3 and human epithelial cell adhesion molecule (EpCAM).

Conclusion

The potential role for targeted therapies in ovarian cancer will be established over the next five to 10 years and already there are a number of Phase III clinical trials underway.

Bevacizumab and other agents that target VEGF or its receptor have demonstrated activity in both platinum-sensitive and platinum-resistant disease. It remains to be determined whether there is an additional benefit for combining bevacizumab or cediranib with chemotherapy, above chemotherapy alone, for first or second line therapy.

At present, there is no effective maintenance strategy for patients following chemotherapy. With the exception of one trial with paclitaxel, other maintenance trials have not demonstrated an improvement in progression-free survival nor overall survival, and increased toxicity has been reported. Ongoing Phase III trials are testing three agents, bevacizumab, cediranib and erlotinib in this setting. With the exception of the EORTC 00541 trial, maintenance treatment will follow the combination of chemotherapy with the investigational agent. The GOG 218 will provide some information as to the relative effect of bevacizumab in combination with chemotherapy, and then as a maintenance therapy.

Each of these trials has a quality of life component incorporated. This is extremely important when we consider that patients who may have few or no disease related symptoms after chemotherapy, may remain on maintenance therapy for extended periods.

Early results with PARP inhibitors are promising and have entered Phase II trials. At present these trials are recruiting an enriched population with known mutation in BRCA1 or BRCA2. In addition, these agents theoretically have the potential to have a synergistic effect with chemotherapy by inhibiting mechanisms of DNA repair. If efficacy is confirmed in mutation-positive patients, then testing on a wider ovarian cancer population would be worthy of evaluation.

Ongoing translational research projects should continue to be incorporated into clinical trials to further our understanding of the mechanisms that drive tumour growth, as well as identify potential predictive factors for response to new investigational agents.

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