



**REGIONAL DRUG AND THERAPEUTICS CENTRE  
(NEWCASTLE)**

**BEVACIZUMAB IN THE TREATMENT OF  
PLATINUM-RESISTANT OVARIAN CANCER**

**Wolfson Unit  
Claremont Place  
Newcastle upon Tyne  
NE2 4HH**

**February 2010**





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## ABOUT THIS REPORT

This is one of a series of evaluations prepared for the Greater Manchester Medicines Management Group by the Regional Drug and Therapeutics Centre (Newcastle). The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by local NHS personnel and appropriate external specialists. However, responsibility for the content and conclusions rests solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

<i>Subject</i>	<i>Date issued</i>
The use of panitumumab in the management of metastatic colorectal cancer	June 2009
The use of ibritumomab as consolidation therapy after remission induction in previously untreated follicular lymphoma	May 2009
The use of azacitidine for the management of myelodysplastic syndromes	May 2009
The use of aprepitant for the prevention of chemotherapy induced nausea and vomiting	March 2009
Current therapeutic strategies for pulmonary arterial hypertension	March 2009
The use of lapatinib in the management of metastatic breast cancer	November 2008
The use of liposomal doxorubicin in the management of metastatic breast cancer	October 2008
The use of dasatinib in the management of acute lymphoblastic leukaemia in adults	August 2008
The use of bevacizumab in the management of metastatic breast cancer <b>(N)</b>	September 2007
The use of entecavir in the management of chronic hepatitis B infection <b>(N)</b>	March 2007
The use of natalizumab in the management of multiple sclerosis <b>(N)</b>	March 2007
The use of aromatase inhibitors in the treatment of early stage breast cancer <b>(N)</b>	March 2007
Palonosetron for the prevention of nausea and vomiting associated with cancer chemotherapy	March 2007
Alemtuzumab in the management of chronic lymphocytic leukaemia	March 2007
Omalizumab in the management of severe, persistent, allergic asthma <b>(N)</b>	June 2006
Bortezomib second-line in the management of multiple myeloma <b>(N)</b>	March 2006

*Older reports are available via our website or on request*

Agents which have been reviewed by the National Institute for Health and Clinical Excellence (NICE) are indicated by **(N)** after the report name. Please refer to the NICE website to access their guidance for these agents/conditions.

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## SUMMARY

- Ovarian cancer is the fifth most common cancer in females and the fourth leading cause of cancer mortality in women in the UK. In 2006, there were 6,596 cases diagnosed in the UK and 4,317 women died from the disease in 2007.
- Initially, ovarian cancer is treated with surgery followed by chemotherapy with either paclitaxel and a platinum compound, or a platinum-based regimen alone. Despite an overall response of 70% - 80% the majority of patients eventually experience a relapse and develop drug-resistant disease. Treatment options for patients with platinum-resistant ovarian cancer are limited.
- Topotecan has shown significant activity in patients with platinum-resistant disease with overall response rates of 7% to 18%. However, it is associated with significant myelosuppression and requires intravenous administration for five days every three weeks.
- Angiogenesis is pivotal in the growth and development of ovarian cancer. Bevacizumab is a recombinant monoclonal antibody that inhibits vascular endothelial growth factor (VEGF)-induced angiogenesis and tumour growth. This report reviews the efficacy and safety of bevacizumab in combination with cyclophosphamide as a substitute for topotecan in the treatment of patients with platinum-resistant ovarian cancer.
- The response rate (RR), progression-free survival (PFS) and overall survival (OS) with bevacizumab plus cyclophosphamide treatment compare favourably with topotecan in this patient group. In single-agent studies RRs of 16% and 21% were reported with bevacizumab. Further data support the potential clinical benefit of combining cyclophosphamide with bevacizumab, with RRs of 24% to 53%. However, there is currently no clear evidence that this regimen is superior to bevacizumab alone in terms of improved PFS or OS.
- The toxicity profile of bevacizumab appears to be superior to that of standard topotecan therapy. Bevacizumab is generally well tolerated with acceptable rates of hypotension, proteinuria and thrombosis, which occur at rates similar to those observed in the treatment of other solid tumours. However, bevacizumab is associated with a significantly higher incidence of gastrointestinal perforation (GIP) in patients with ovarian cancer (3% to 11%) compared to those with other cancers (1% to 2%).
- The current acquisition cost of bevacizumab is £242.66 per 100 mg/4ml vial and £924.40 per 400 mg/16ml vial (excluding VAT). Assuming a mean adult female body weight of 58 kg, the total cost of bevacizumab per patient per 10mg/kg fortnightly dose would be £1,409.72. These costs do not take into account the additional cost of oral cyclophosphamide (~ £0.14 per day).
- The current acquisition cost of topotecan is £97.65 per 1 mg vial and £290.62 per 4 mg vial. For a female with a body surface area of 1.63 m<sup>2</sup> the acquisition cost of topotecan is £969.51 per cycle (excluding premedication and VAT).

## BACKGROUND

Ovarian cancer is the fifth most common cancer in females in the UK.<sup>1</sup> In 2006 there were 6,596 cases of ovarian cancer diagnosed in the UK, representing an age-standardised incidence of 16.9 per 100,000 women.<sup>1</sup> Ovarian cancer is the fourth leading cause of cancer mortality in women with 4,317 deaths in the UK in 2007.<sup>1</sup>

Ovarian cancer is predominantly a disease of older, post-menopausal women with over 80% of cases being diagnosed in women over 50 years, and a median age at diagnosis of 60 years.<sup>1,2</sup> Although the etiology of the disease is largely unknown, women with a strong family history of ovarian cancer are considered to be at high risk of developing it.<sup>1,3</sup> Between five and 10% of all cases occur amongst women who carry mutations in the genes BRCA1 and BRCA2, or who carry the hereditary non-polyposis colorectal cancer (HNPCC) gene.<sup>1-3</sup> For a woman with a BRCA1 or BRCA2 mutation the cumulative risks of developing ovarian cancer by the age of 70 are 40% (95% confidence interval [CI], 35% to 46%) and 18% (95% CI, 13% to 23%), respectively.<sup>4</sup> Other factors suspected to be associated with an increased risk of ovarian cancer include nulliparity, early menarche, late menopause and infertility.<sup>1,2,5</sup> Conversely, oral contraceptive use, pregnancy, breast feeding and tubal ligation are associated with a reduced risk.<sup>1,2</sup>

### **CLASSIFICATION AND PROGNOSIS**

Ovarian cancers are classified according to the primary cell type from which they derive.<sup>2,6</sup> Epithelial tumours arise from cells lining or covering the ovaries and account for about 80% of all ovarian cancers. Germ and stromal cell tumours each account for around a further 10% of cases.<sup>6</sup> Surgical staging is described according to the International Federation of Gynaecologists and Obstetricians (FIGO) criteria, in which early-stage disease is confined to the ovaries and advanced-stage disease has spread beyond the ovaries (Appendix 1).<sup>7</sup>

The symptoms of ovarian cancer are often non-specific and difficult to distinguish from other conditions. The most common symptoms include abdominal pain and bloating, fatigue, weight loss, urinary symptoms and occasionally abnormal vaginal bleeding.<sup>1,3</sup> If ovarian cancer is suspected on the basis of history and physical examination then urgent referral should be made to a dedicated diagnostic centre. The Risk of Malignancy Index (RMI) using transvaginal ultrasound examination, menopausal status (M) and blood levels of the ovarian cancer marker CA-125 is a highly reliable diagnostic aid in the preoperative assessment of ovarian carcinomas.<sup>1-3</sup>

The stage of disease at diagnosis is the most important factor in predicting overall survival (OS) and the risk for recurrence or relapse.<sup>1</sup> Other established prognostic which may influence both survival and response to treatment include level of residual disease after debulking surgery, the grade and histology of the tumour, good performance status, and age at diagnosis.<sup>2,8</sup>

The five-year survival rate for women diagnosed with stage I disease may be as high as 90% and for stage II approaches 70%.<sup>9</sup> However, ovarian cancer is often difficult

to diagnose in the early stages due to the often non-specific nature of the symptoms.<sup>1,3</sup> Consequently,  $\geq 70\%$  of cases are not diagnosed until the disease is at an advanced stage when it has metastasised, or spread, to other abdominal organs (FIGO stages III and IV).<sup>6,9</sup> As a result the five-year survival rate for these women remains less than 30%.<sup>9,10</sup>

### **CURRENT SERVICE PROVISION**

The standard, NICE-approved, management of advanced ovarian cancer is primary debulking surgery to enable complete surgical staging, followed by adjuvant systemic chemotherapy.<sup>11</sup> Initial surgery should be a comprehensive staging laparotomy, including a total abdominal hysterectomy (TAH), and bilateral salpingo-oophorectomy (BSO) along with systematic examination and sampling of all at-risk tissues.<sup>2,8,9</sup> However, in most women complete removal of the tumour is not usually possible and further therapy is required in the majority of patients. Radiotherapy is of limited benefit in the treatment of ovarian cancer and is associated with significant adverse effects on other abdominal organs.<sup>11</sup>

NICE guidance currently recommends that either paclitaxel in combination with a platinum-based compound, or a platinum-based regimen alone (cisplatin or carboplatin) should be the standard initial therapy for patients with ovarian cancer following cytoreductive surgery.<sup>11</sup> Although these regimens yield overall responses in approximately 70% to 80% of patients, the majority of patients (55% to 75%) will experience a relapse within two years of completing treatment and require second-line chemotherapy.<sup>6,9</sup> The long-term prognosis for these patients is poor and should be regarded as palliative in intent, with the aims of reducing symptoms, prolonging survival and maintaining quality of life.<sup>3,6,12</sup>

For the purpose of guiding the choice of second-line chemotherapy, the time to relapse after initial chemotherapy (treatment-free interval) has been widely adopted to stratify patients into four groups:<sup>13</sup>

- **Platinum-sensitive disease:** patients who relapse 12 months or more after completion of initial platinum-based chemotherapy
- **Partially platinum-sensitive disease:** patients who relapse between six and 12 months after completion of initial platinum-based chemotherapy
- **Platinum-refractory disease:** patients who relapse during or immediately following initial platinum-based chemotherapy
- **Platinum-resistant disease:** patients relapsing under six months from completion of initial platinum-based chemotherapy

Currently, it is usual to re-challenge patients who have platinum-sensitive disease with chemotherapy that includes a platinum compound.<sup>13</sup> NICE guidance recommends paclitaxel in combination with a platinum-based compound (carboplatin or cisplatin) as a second-line (or subsequent) treatment option for women with platinum-sensitive or partially platinum-sensitive disease.<sup>13</sup> Where patients have received paclitaxel as part of their first-line treatment, paclitaxel may be considered

as an option for their second-line (or subsequent) treatment.<sup>13</sup> The guidance recommends pegylated liposomal doxorubicin hydrochloride (PLDH) as a further treatment option for women with platinum-sensitive disease.<sup>13</sup>

Non-platinum-based regimens are recommended by NICE for the treatment of women with platinum-refractory or platinum-resistant disease.<sup>13</sup> Single-agent paclitaxel and PLDH are both recommended as options for the initial treatment, or subsequent treatment of women with platinum-refractory or platinum-resistant disease. Topotecan is only recommended for the treatment of women with platinum-refractory or platinum-resistant ovarian cancer if PLDH and paclitaxel are considered unsuitable.<sup>13</sup>

## **BEVACIZUMAB**

Bevacizumab (Avastin<sup>®</sup> Roche Products Ltd) is a humanized recombinant monoclonal antibody targeting vascular endothelial growth factor (VEGF).<sup>14</sup> VEGF is one of the most potent and specific mediators of angiogenesis and plays a significant role in initiating and mediating tumour growth.<sup>15,16</sup> Over-expression of VEGF is frequently observed in patients with ovarian cancer and is associated with a poor prognosis.<sup>15,16</sup> In addition to stimulating angiogenesis, VEGF also induces vascular permeability which is thought to be crucial in the development of ascites in ovarian cancer.<sup>17,18</sup> Bevacizumab prevents VEGF from binding to and activating its receptors on the surface of vascular endothelial cells, thereby inhibiting VEGF-induced angiogenesis and tumour growth.

The purpose of this report is to review the efficacy and safety of bevacizumab in combination with cyclophosphamide as a substitute for topotecan in the treatment of patients with platinum-resistant ovarian cancer.

Bevacizumab is not currently licensed for the treatment of ovarian cancer.

## **EFFICACY**

### **BEVACIZUMAB PLUS CYCLOPHOSPHAMIDE**

Three trials have examined the efficacy of bevacizumab plus cyclophosphamide in patients with platinum-resistant ovarian cancer.<sup>17,19,20</sup> In a Phase III trial conducted by Chura et al., fifteen patients with recurrent ovarian cancer were treated with a combination of intravenous bevacizumab 10 mg/kg every other week plus oral cyclophosphamide 50 mg daily until disease progression or undue toxicity.<sup>17</sup> All patients had been heavily pretreated with standard second-line chemotherapeutic agents. Eleven patients were initially platinum resistant, but all were secondarily resistant at the time of study treatment. The median number of previous chemotherapy regimens was eight (range, 5 – 15), with a median time from initial diagnosis to treatment with bevacizumab of 68.9 months (range, 26.5 – 177.2). The median age was 57 years (range, 42 – 69).

The primary endpoint was response rate determined by CA-125 serum tumour marker levels or changes in target lesions according to Response Evaluation Criteria in Solid Tumours (RECIST).<sup>21</sup> Secondary outcome measures included duration of response and progression free survival (PFS). The median number of infusions of

bevacizumab was eight (range, 2 – 12). There was a complete response after four months of therapy in two patients (13%; 95% CI, -3.9% to 30.5%). Six patients experienced a partial response (40%; 95% CI, 15.2% to 64.8%). Three patients had stable disease (2%; 95% CI, -0.24% to 40.2%) of 4.0, 5.2 and 5.5 months duration. The median PFS for all patients was 3.9 months (range, 0 to 10.4 months). Among the 11 patients who experienced benefit the median PFS was 4.4 months (range, 2.3 to 10.4 months), with a PFS of 18% at six months (13% for all patients).

Garcia et al's. Phase III study evaluated IV bevacizumab 10mg/kg every other week (weekly for the first three weeks) plus oral cyclophosphamide 50 mg daily in 70 patients with recurrent ovarian cancer.<sup>19</sup> All patients had received prior therapy with platinum and a taxane. Twenty-eight patients (40%) had platinum-resistant disease based on their initial therapy. The median number of previous chemotherapy regimens was two (range, 1 – 3), and the median age was 60 years (range, 31 – 83).

The primary endpoint was PFS, and secondary outcome measures included response rate assessed by CA-125 levels or RECIST.<sup>21</sup> At the time the data were analysed, the median follow-up period was 23.2 months (range, 3.7 – 32.7). In all patients the median PFS was 7.2 months (95% CI, 5.3 to 8.7), with a median OS of 16.9 months (95% CI, 11.4 to 25.2). There was a statistically significant difference in PFS and OS between the platinum-sensitive and platinum-resistant patients ( $p=0.004$  and  $p=0.017$ , respectively). Although no exact figures are reported, extrapolation of data from the presented Kaplan-Meier curves suggest an estimated median PFS of ~24.4 months for platinum-sensitive and ~11.5 months for platinum-resistant patients. The corresponding estimates for OS were ~8.0 months and ~4.5 months, respectively. No patients achieved a complete response, but 17 achieved a partial response (24%; 95% CI, 15% to 36%). Forty-four patients had stable disease (63%; 95% CI, 50% to 74%). There was no significant difference between the response rates of the platinum-sensitive and platinum-resistant patients (33% vs. 12%, respectively;  $p=0.074$ )

Jurado et al. reported data from a review of nine heavily-pretreated patients with advanced ovarian cancer who received treatment with IV bevacizumab 10 mg/kg every other week plus oral cyclophosphamide 50 mg daily.<sup>20</sup> All patients had measurable disease. Eight (88%) patients were platinum-resistant, and one was platinum-sensitive. Of the former, two had developed resistance after first-line, five after second-line and one following third-line platinum-based therapy. The median number of previous chemotherapy regimens was five (range, 2 – 7), and the median age was 54 years (range, 37 – 61).

The primary endpoints were response rate, response duration and PFS. Response was assessed by CA-125 levels or RECIST.<sup>21</sup> An objective response was observed in four patients (44%), with two (22%) achieving a complete response and a further two (22%) a partial response. Two patients (22%) had stable disease for over three months duration. The median PFS for all patients was 5.5 months (range, 4.5 to 5.5), and median OS was 9 months (95% CI, 3 to 15).

### **SINGLE-AGENT BEVACIZUMAB**

Two phase II trials have examined the efficacy of single-agent bevacizumab in patients with platinum-resistant ovarian cancer.<sup>18</sup> Cannistra et al., evaluated IV bevacizumab 15 mg/kg every three weeks in patients with platinum-resistant recurrent ovarian or peritoneal serous cancer.<sup>18</sup> The study was initially designed to include approximately 120 patients, but was closed early after enrolment of 44 patients, because of a higher than expected incidence of gastrointestinal perforation (GIP). All 44 patients included in the study had platinum-resistant disease, of whom 37 (87.8%) were primarily platinum-resistant. Around half (47.7%) had received three prior chemotherapy regimens, and the median age was 59.5 years (range, 31 – 87).

The primary endpoint was objective response rate determined by CA-125 levels or RECIST.<sup>21</sup> Secondary outcome measures included duration of PFS and OS. At the time the data were analysed the median follow-up period was 10.2 months. The median number of infusions of bevacizumab was five (range, 2 – 16). No patients achieved a complete response, but seven achieved a partial response (15.9%; 95% CI, 7.2% to 29%). Twenty-seven patients (61.4%) had stable disease, with 11 of these remaining stable for at least three months. For the seven patients achieving a response, the median PFS was 4.2 months (range, 1.7 to 9.2 months). In all patients the median PFS was 4.4 months (95% CI, 3.1 to 5.5 months), and median OS was 10.7 months (95% CI, 3 to 15).

The second study by Burger et al. included a total of 62 patients with persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer.<sup>22</sup> Recruitment was restricted to patients who had received only one (66%) or two (34%) prior chemotherapy regimens. Thirty-six (58%) patients were platinum-resistant, and 26 (42%) were platinum-sensitive. Treatment consisted of bevacizumab 15 mg/kg every three weeks until disease progression or unacceptable toxicity, and the median age was 57 years (range, 18 – 79).

The primary endpoints were PFS at six months and clinical response by RECIST.<sup>21</sup> Secondary outcomes assessed the potential impact of prognostic variables (initial performance status, platinum sensitivity, number of prior regimens, age) on the hazard of progression or death. The median number of infusions of bevacizumab was seven (range, 1 – 16). The overall response rate was 21% (90% CI, 12.9% to 31.3%), with two patients (3%) achieving a complete response and 11 (18%) a partial response. An additional 27 patients (61.4%) had stable disease. Twenty five patients (40.3%) were progression free at six months (90% CI, 29.8% to 53.6%). The median PFS in all patients was 4.7 months and median OS was approximately 16.9 months. An exploratory analysis of prognostic factors for PFS showed no statistically significant association between platinum sensitivity and the hazard of progression.

### **TOPOTECAN**

Several phase II studies have demonstrated the single-agent activity of topotecan as second-line therapy in relapsed ovarian cancer.<sup>23-27</sup> Overall response rates in these studies ranged from 12% to 18% in patients with platinum-resistant recurrent ovarian cancer.<sup>23,26</sup> Stable disease was reported in 18% to 61% of these patients.<sup>23,24</sup> In those patients achieving benefit the median duration of response ranged from 4.5 months to 8.9 months.<sup>24,25</sup> Median OS ranged from six to 10 months.<sup>25,26</sup>

The efficacy of topotecan in the treatment of advanced or recurrent ovarian cancer has been further demonstrated in three large, phase III randomised trials.<sup>10,12,28,29</sup> In a study comparing the efficacy of topotecan with paclitaxel (n=226) there were no statistically significant differences between the two groups in terms of response rate (21% vs. 13%, respectively),<sup>28</sup> duration of response (32 vs. 20 weeks), time to progression (19 vs. 15 weeks),<sup>29</sup> or OS (63 vs. 53 weeks).<sup>29</sup> In platinum-resistant patients the corresponding response rates were 13% vs. 7%, respectively.<sup>28</sup> In a comparative study of topotecan versus PLDH there were no statistically significant differences between the two groups in terms of response rate (17% vs. 20%), PFS (16 vs. 17 weeks) or OS (57 vs. 60 weeks).<sup>12</sup> In platinum-resistant patients the corresponding response rates were 7% vs. 12%, respectively.<sup>12</sup> There was a statistically significant benefit in favour of intravenous topotecan for OS compared to participants treated with oral topotecan (58 vs. 51 weeks; p=0.033). However, no further significant differences between the two groups were found for response rate (20% vs. 13%), response duration (26 vs. 34 weeks) or time to progression (17 vs. 13 weeks).<sup>10</sup> In platinum-resistant patients the corresponding response rates were 11% vs. 8%, respectively.<sup>10</sup>

## ADVERSE EFFECTS

### BEVACIZUMAB

The overall safety profile of bevacizumab in the treatment of patients with platinum-resistant ovarian cancer is consistent with that observed in the treatment of other types of cancer.<sup>14</sup> The most common grade 3 or 4 adverse events associated with the combined bevacizumab and cyclophosphamide regimen were hypertension (16%), proteinuria (4%) and thrombosis (3%).<sup>19</sup> In single-agent studies the most common grade 3 or 4 adverse events were proteinuria (16%), hypertension (9%) bleeding (2%) and wound-healing complications (2%).<sup>18</sup>

Gastrointestinal perforation (GIP) is an uncommon but well documented adverse event associated with bevacizumab treatment, with an incidence of 1% to 2% reported by the manufacturer across all studies.<sup>14</sup> The rates of GIP reported in the studies of bevacizumab in advanced ovarian cancer vary considerably. Three studies reported no GIP in patients treated with bevacizumab alone (n=62),<sup>22</sup> or in combination with cyclophosphamide (n=24).<sup>17,20</sup> However, the study by Cannistra et al. was closed prematurely after 11% of patients treated with single-agent bevacizumab developed GIP (n=44).<sup>18</sup> Garcia et al. reported an incidence of 3% in patients treated with the combination regimen (n=70).<sup>19</sup> The reasons for the increased incidence of GIP associated with bevacizumab in the treatment of ovarian cancer are not known and the numbers are too small to draw any definitive conclusions, but differences in patient characteristics are likely to be of relevance. The incidence of GIP appears to be higher in heavily pre-treated patients,<sup>19</sup> and a trend toward higher risk of GIP was observed for patients with bowel wall thickening or bowel obstruction on CT scan.<sup>18</sup>

## TOPOTECAN

The dose-limiting toxicity associated with intravenous topotecan treatment is myelosuppression. Severe neutropenia, thrombocytopenia and moderate to severe anaemia occur in substantial numbers of patients. However, these adverse events are usually predictable, of short duration, non-cumulative, and manageable with dose reduction and dose delay. A summary of haematological adverse events associated with topotecan in the treatment of ovarian cancer are shown in table 1.

Table 1. Summary of grade 3 or 4 adverse events of topotecan therapy.<sup>10,12,28,29</sup>

Haematological	Grade 3	Grade 4
Neutropenia	11% -15%	62% - 84%
Leucopenia	35% - 60%	15% - 31%
Thrombocytopenia	17% - 28%	17% - 18%
Anaemia	25% - 38%	4% - 8%

The non-haematological toxicity associated with topotecan treatment is generally mild and not dose-limiting, with grade 3 or 4 adverse events occurring in less than 10% of patients.<sup>30</sup> Among all patients receiving topotecan in clinical trials the most frequently reported non-haematological adverse events were gastrointestinal such as nausea (52%), vomiting (32%), diarrhoea (18%), constipation (9%) and mucositis (15%). Fatigue has been reported in around 25% and asthenia in 16% of patients whilst receiving topotecan. Total or pronounced alopecia has been observed in 30% of patients and partial alopecia in 15%. Hypersensitivity reactions have been reported rarely.<sup>30</sup>

Because of the major toxicity associated with standard topotecan therapy alternative doses and schedules have been investigated with the goal of improving tolerability while maintaining or improving activity.<sup>31,32</sup> Reducing the starting topotecan dose to 1.0 or 1.25 mg/m<sup>2</sup> is recommended to reduce the incidence of severe myelosuppression in individuals receiving topotecan for five consecutive days. Alternative schedules of 3-day or weekly dosing may also reduce the incidence of myelosuppression.<sup>31,32</sup>

## DOSAGE, ADMINISTRATION AND COST

### BEVACIZUMAB

In trials using combination therapy in patients with platinum-resistant ovarian cancer, treatment consisted of intravenous bevacizumab 10 mg/kg every two weeks plus oral cyclophosphamide 50 mg daily.<sup>17,19,20</sup> Due to the possible risk of infusion reactions the first dose of bevacizumab should be administered over 90 minutes as an IV

infusion following chemotherapy.<sup>14</sup> If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. Bevacizumab should not be administered as an IV push or bolus. If well tolerated, it is expected that treatment will continue until disease progression occurs.

The current acquisition cost of bevacizumab is £242.66 per 100 mg/4ml vial and £924.40 per 400 mg/16ml vial (excluding VAT).<sup>33</sup> Assuming a mean adult female body weight of 58 kg,<sup>34</sup> the total cost of bevacizumab per patient per 10mg/kg fortnightly dose would be £1,409.72. These costs do not take into account the additional cost of oral cyclophosphamide treatment (~ £0.14 per day).<sup>33</sup> The overall cost depends on the number of cycles per patient undertaken. Costs may vary in different settings because of negotiated procurement discounts.

### **TOPOTECAN**

The recommended dose of topotecan for the treatment of ovarian cancer is 1.5 mg/m<sup>2</sup> of the patient's body surface area per day, administered by intravenous infusion over 30 minutes daily for five consecutive days, with a three-week interval between the start of each course.<sup>30</sup> If well tolerated, treatment may continue until disease progression occurs.

The current acquisition cost of topotecan is £97.65 per 1 mg vial and £290.62 per 4 mg vial.<sup>33</sup> For a female with a body surface area of 1.63 m<sup>2</sup> the acquisition cost of topotecan is £969.51 per cycle (excluding premedication and VAT). The overall cost depends on the number of cycles per patient undertaken. Costs may vary in different settings because of negotiated procurement discounts.

### **PLACE IN TREATMENT**

Treatment options for patients with platinum-resistant ovarian cancer are limited. Current NICE guidance recommends single-agent paclitaxel or PLDH for the treatment of women with platinum-resistant ovarian cancer.<sup>13</sup> NICE has approved topotecan for the treatment of platinum-resistant disease only when paclitaxel and PLDH are considered unsuitable.<sup>13</sup> Topotecan has shown significant activity in patients with platinum-resistant disease with overall response rates of 7% to 18%.<sup>10,12,23-28</sup> However, topotecan is associated with significant myelosuppression, particularly in heavily pretreated patients, and requires IV administration for five days every three weeks.

Numerous studies have shown that bevacizumab has significant activity in recurrent ovarian cancer, including in individuals with well-characterized platinum-resistant disease. The overall response, time to progression and median survival observed with bevacizumab treatment compare favourably with topotecan therapy in this patient group. Two trials have confirmed the single-agent activity of bevacizumab, reporting response rates of 16% and 21%.<sup>18,22</sup> Further data support the potential clinical benefit of combining cyclophosphamide with bevacizumab, with response rates of 24% to 53%.<sup>17,19,20</sup> However, there is currently no clear evidence that this regimen is superior to bevacizumab alone in terms of improved PFS or OS.

The management of chemotherapy-induced toxicity is a major consideration in the treatment of patients with recurrent ovarian cancer. The toxicity profile of bevacizumab appears to be superior to that of standard topotecan therapy. Bevacizumab is generally well tolerated with acceptable rates of hypotension, proteinuria and thrombosis,<sup>19</sup> which occur at rates similar to those observed in the treatment of other solid tumours.<sup>14</sup> However, bevacizumab is associated with a significantly higher incidence of GIP in patients with ovarian cancer (3% to 11%)<sup>18,19</sup> compared to those with other cancers (1% to 2%).<sup>14</sup> It has been suggested that this serious adverse event may be particularly relevant when bevacizumab is administered to heavily pre-treated patients and/or those with evidence of significant involvement of tumour with the bowel wall.<sup>18</sup> Thus, further examination of this issue will be necessary in order to define the populations at risk and determine how to minimise this potential hazard. It is possible that such life-threatening complications may be avoidable by careful patient selection, and this would entail that the numbers eligible for treatment in Christies Hospital NHS Trust may be around 10-15 per year only.<sup>35</sup>

Although drug procurement costs are slightly higher with bevacizumab than topotecan, the administration costs are cheaper given that topotecan requires five daily intravenous infusions every three weeks compared to a single intravenous infusion every two weeks with bevacizumab.

Bevacizumab is not licensed for the treatment of ovarian cancer, but is currently in phase III development for the first-line treatment of ovarian cancer with an anticipated filling date of late 2011.<sup>36</sup> Due to the limited number of patients with platinum-resistant disease and in light of current NICE guidance it is not anticipated that a marketing authorisation will be sought for this specific indication.<sup>36</sup>

## **ARRANGEMENTS FOR PRESCRIBING**

Bevacizumab should only be used in units specialised in the administration of cytotoxic chemotherapy and should only be administered under the supervision of a physician experienced in the use of chemotherapy. The choice of treatment for chemotherapy should be made after discussion between the responsible clinician and the patient about the risks and benefits of the options.

## **FUTURE DEVELOPMENTS**

Bevacizumab is currently in Phase III development for the first- and second-line treatment of ovarian cancer.<sup>37</sup>

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## **APPENDICES**

**Appendix I.** *International Federation of Gynaecologists and Obstetricians (FIGO) staging system for ovarian cancer.*<sup>7</sup>

### **Stage I - The cancer is confined to the ovaries**

**IA** - Limited to one ovary and the outer ovarian capsule is intact. There is no tumour on the external surface of the ovary and there are no malignant cells in ascites or peritoneal washings.

**IB** - Cancer is present in both ovaries and the outer ovarian capsule is intact. There is no tumour on the external surface of the ovary and there are no malignant cells in ascites or washings.

**IC** – Tumour limited one or both ovaries with capsule rupture or there is tumour on the ovarian surface or malignant cells are present in ascites or washings.

### **Stage II – The cancer has spread to other pelvic organs or surfaces**

**IIA** - Extension or implants onto the uterus and/or fallopian tube. The washings are negative and there is no ascites.

**IIB** - Extension or implants onto other pelvic tissues. The washings are negative and there is no ascites.

**IIC** - Pelvic extension or implants with malignant cells in ascites or washings.

### **Stage III – The cancer has spread outside the pelvis to the abdominal area, including or the lymph nodes**

**IIIA** - Tumour is largely confined to the pelvis but with microscopic peritoneal metastases beyond pelvis.

**IIIB** - Macroscopic peritoneal metastases beyond pelvis  $\leq 2$  cm in size

**IIIC** - Peritoneal metastases beyond pelvis,  $>2$  cm or regional lymph node metastases, or both.

### **Stage IV – The cancer has spread to distant organs such as the liver, chest or brain**

## SUMMARY TABLE OF KEY STUDIES

Key: AEs – adverse events; CI – confidence interval; CNS – central nervous system; CR – complete response; DVT – deep vein thrombosis; EOC – Eastern Cooperative Oncology Group; EOC – epithelial ovarian cancer GI – gastrointestinal; GOC – Gynaecologic Oncology Group; IV – intravenously; MI – myocardial infarction; OL – open label; OR – objective response; OS – overall survival; P – prospective; pts – patients; PFS – progression free survival; PR – partial response; PSC – peritoneal serous cancer; RECIST – Response Evaluation Criteria in Solid Tumours; R – retrospective review; SD – stable disease.

### Bevacizumab plus cyclophosphamide

Reference	Design	Intervention	Patient numbers	Inclusion criteria	Exclusion criteria	Primary outcome	Results	Adverse events
Chura 2007. <sup>17</sup>	P, Phase II	Bevacizumab 10 mg/kg IV every other week plus oral cyclophosphamide 50 mg daily.	n=15  secondarily platinum-resistant at time of treatment, n=14	Heavily pretreated pts with recurrent ovarian cancer, failed standard second line therapies and/or had inadequate bone marrow reserve to tolerate traditional cytotoxic regimens.	Uncontrolled hypertension, pre-existing proteinuria, recent surgery or findings consistent with small bowel obstruction.	Response rates (RECIST).  Secondary outcomes included duration of response and PFS.	CR = 13.3%; 2/15 pts (95% CI, -3.9% to 30.5%).  PR = 40.0%; 6/15 pts (95% CI, 15.2% to 64.8%).  SD = 2.0%; 3/15 pts (95% CI, -0.24% to 40.2%).  Median PFS = 3.9 months (range 0 to 10.4).	Grade 3 or 4 diarrhoea occurred in two pts, grade 3 pancreatitis in one, grade 1 bleeding (epistaxis and gingival) in two, and grade 2 proteinuria and hypertension in one.  No GI perforations or fistulas reported.

Reference	Design	Intervention	Patient numbers	Inclusion criteria	Exclusion criteria	Primary outcome	Results	Adverse events
Garcia 2008. <sup>19</sup>	P, Phase II	Bevacizumab 10mg/kg IV initially every week followed by every two weeks, plus oral cyclophosphamide 50 mg daily.	n=70  platinum-resistant n=28	Histologically documented recurrent epithelial ovarian cancer or primary peritoneal carcinoma with measurable disease by RECIST, received a platinum-containing regimen for primary disease and up to two distinct prior regimens for recurrent disease, an ECOG performance status of 0 to 2, and adequate haematological, renal and hepatic function.	Serious non-healing wound ulcers, bone fractures, major surgical procedure, recent open biopsy, significant traumatic injury, history of DVT, recent arterial thrombosis, full dose anticoagulants, history or evidence of CNS disease, significant cardiovascular or peripheral vascular disease, and prior treatment with an antiangiogenic agent.	PFS  Secondary outcomes included response rates (RECIST), and OS.	In all pts (n=70) the median PFS = 7.2 months (95% CI, 5.3 to 8.7) and median OS =16.9 months (95% CI, 11.4 to 25.2).  The estimated probability of being alive and progression free at six months was 56% (95% CI, 44% to 67%). There was a significant difference in PFS and OS between platinum-sensitive and platinum-resistant pts (p=0.004 and p=0.017, respectively).  CR = none; 0/70 pts PR = 24%; 17/70 pts (95% CI, 15% to 36%) SD = 63%; 44/70 pts (95% CI, 50% to 74%)	The most common bevacizumab-related AEs were hypotension and proteinuria (39% and 44%, respectively).  Four pts (6%) developed GI perforation, and one patient each a GI fistula, wound healing complication, and grade 3 GI bleeding.  There were three treatment-related deaths; two associated with pulmonary hypertension and one with obstruction and GI perforation.

Reference	Design	Intervention	Patient numbers	Inclusion criteria	Exclusion criteria	Primary outcome	Results	Adverse events
Jurado 2008. <sup>20</sup>	R	Bevacizumab 10mg/kg IV initially every two weeks, plus oral cyclophosphamide 50 mg daily.	n=9  platinum-resistant n=8	Histologically documented epithelial ovarian cancer which had failed to respond to platinum-based chemotherapy, ECOG performance status of 0 to 2, and adequate haematological, renal and hepatic function.	Not stated	Response rates (RECIST) and PFS.	OR = 44%; 4/9 pts CR = 22%; 2/9 pts PR = 22%; 2/9 pts SD = 22%; 2/9 pts  Median PFS = 5.5 months (95% CI, 4.5 to 6.5) Median OS = 9 months (95% CI, 3 to 15).	One patient developed grade 3 haematuria and grade 3 abdominal pain. Other AEs included epistaxis (22%), hypertension, mucositis and dyspnoea, all 11%.

## Single-agent bevacizumab

Reference	Design	Intervention	Patient numbers	Inclusion criteria	Exclusion criteria	Primary outcome	Results	Adverse events
Cannistra 2007. <sup>18</sup>	P, Phase II	Bevacizumab IV 15mg/kg every 3 weeks	n=44*  platinum-resistant n=44  * The study was designed to include ~120 pts, but was closed early after 44 pts had enrolled.	Platinum-resistant EOC or PSC measurable by RECIST, received ≤3 prior treatment regimens, ECOG performance status of 0 or 1, and adequate bone marrow, renal and hepatic function.	Brain metastases or history of other malignancies within 5 years before study entry, uncontrolled hypertension, unstable angina, congestive heart failure, MI, stroke, or transient ischaemic attack within 6 months, vascular disease, major surgery within 28 days, symptoms of intestinal obstruction, abdominal fistula or GI perforation.	Response rates (RECIST).  Secondary outcomes included PFS and OS.	PR = 15.9%; 7/44 pts (95% CI, 7.2% to 29.0%). SD = 61.4%; 27/44 pts Median PFS = 4.4 months (95% CI, 3.1 to 5.5) Median OS = 10.7 months.	The study was stopped early due to a higher than expected incidence of GI perforation (11.4%; 5/44 pts).  The most common bevacizumab-related grade 3 or 4 AEs included proteinuria (15.9%), hypotension (9.1%), bleeding (2.3%) and wound-healing complications (2.3%).  Three deaths were related to bevacizumab treatment: one MI and cerebrovascular ischaemia, one intestinal perforation, and one hypertensive encephalopathy.

Reference	Design	Intervention	Patient numbers	Inclusion criteria	Exclusion criteria	Primary outcome	Results	Adverse events
Burger 2007. <sup>22</sup>	P, Phase II	Bevacizumab IV 15mg/kg every 3 weeks	n=62  platinum-resistant n=26	EOC or PSC measurable by RECIST, received one or two prior cytotoxic regimens, ECOG performance status of 0 or 1, and adequate haematological, renal and hepatic function.	History of other malignancies within 5 years before study entry, prior non-cytotoxic therapy, non-healing wounds, infection requiring antibiotics, active bleeding, coagulopathy, CNS disease, significant cardiovascular disease, major surgery within 28 days or anticipated while on study, and prior therapy with bevacizumab.	PFS at six months and clinical response rates (RECIST).  Secondary outcomes assessed the potential impact of prognostic variables including: initial performance status, platinum sensitivity, number of prior regimens and age.	PFS at six months =40.3%; 25/62 pts (90% CI, 29.8% to 53.6%).  Median PFS = 4.7 months and median OS = 16.9 months.  OR = 21%; 13/62 pts (90% CI, 12.9% to 31.3%)  CR = 3%; 2/62 pts  PR = 18%; 11/62 pts  SD = 52%; 31/62 pts	The most common bevacizumab-related grade 3 AEs were hypotension (9.7%), pain (4.7%) and hypersensitivity (3.2%). One patient experienced grade 4 proteinuria.  Four pts (6.5%) developed grade 3 or 4 GI events; none experienced GI perforations or fistulae.