NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

[Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of ovarian cancer]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation
NCRI Gynaecological CSG/RCP/RCR/ACP/JCCO

[redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? √
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? √
- other? (please specify)

Please note that Professor Jayson and Dr Hall have research collaborations with Roche and have sat on advisory boards for Roche to discuss the use of bevacizumab in ovarian cancer

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SUMMARY OF RECOMMENDATIONS FOR THIS SUBMISSION

Bevacizumab should be available for use in combination with platinum based, cytotoxic therapy and as maintenance therapy for patients with advanced (FIGO IIIb-IV) inoperable ovarian cancer at presentation or for patients who have any residual disease after primary surgery. In patients who did not initially receive bevacizumab but who have any residual disease after interval surgery (neoadjuvant approach), bevacizumab should be available for the final cycles of treatment and subsequent maintenance therapy. Bevacizumab should be administered at 7.5mg/kg every 3 weeks with cytotoxic chemotherapy and until symptomatic disease progression in patients with any residual disease; or for up to 15 months, in the case of women who achieve a radiological and biochemical complete response.

PROPOSED RECOMMENDATIONS

A synthesis of available randomised trial data suggests that

1. Patients with good performance status (ECOG 0-2) and FIGO stage IIIc/IV ovarian cancer with any residual disease after primary debulking surgery should be offered bevacizumab in addition to carboplatin and paclitaxel, provided there are no contraindications to bevacizumab therapy. Although licensed at 15mg/kg every 3 weeks for 15 months in this setting, the efficacy of the two doses of bevacizumab is identical in the matched subgroups of the two pivotal trials, ICON7 and GOG-218, suggesting that the higher dose of 15mg/kg every 3 weeks is unnecessary. Maintenance therapy is an important component of the effect of bevacizumab and treatment should continue until progression in patients with residual disease; or for up to 15 months in patients who achieve a radiological and biochemical complete response.
2. Patients should be monitored for hypertension and proteinuria and algorithms for the management of bevacizumab-associated hypertension and proteinuria should be developed and standardised. Blood pressure and urinalysis should be measured at each administration of bevacizumab in hospital. The incidence of significant renal impairment is however very low at 2.2% and is reversible on withdrawal of bevacizumab[1].
3. Carboplatin, paclitaxel and bevacizumab can be administered in both cancer centres and units. Significant adverse effects include hypertension in 18% and a slightly higher incidence of bowel toxicity and perforation in the GOG218 trial (2.5% vs 1% in control group). This was not observed in ICON7.
4. Bevacizumab should be permanently discontinued in those who have hypertension that cannot be medically controlled, proteinuria greater than 2g in 24 hours and in rare patients who develop bowel perforation, fistulae or reversible posterior leukoencephalopathy.
5. There is no evidence to support the administration of bevacizumab in the first line setting to patients with low risk disease (no residual disease or low stage and grade) or those with poor performance status. Patients who have contraindications to VEGF inhibitors (see below) can still be considered for treatment with conventional cytotoxic therapy alone.
6. In patients who did not receive bevacizumab during first line therapy and who have a platinum-sensitive recurrence (≥ 6 months treatment free interval),

bevacizumab should be considered as an addition to carboplatin combinations with gemcitabine or paclitaxel. Current evidence suggests a dose of 15mg/kg bevacizumab in this setting every 3 weeks with chemotherapy then as maintenance until progression. The evidence for this arose from a trial in bevacizumab-naïve patients with platinum sensitive recurrent disease[2].

7. In patients with platinum resistant, recurrent ovarian cancer (<6 months treatment free interval after last platinum-containing chemotherapy), a randomised trial has shown a significant improvement in progression free survival in patients receiving cytotoxic chemotherapy with bevacizumab 15mg/kg, every 3 weeks. The majority (92%) had not received prior anti-angiogenic therapy[3].
8. NHS implications: In the UK approximately 3200 patients a year would be eligible for treatment with bevacizumab in combination with carboplatin and paclitaxel, in the first line setting. For these patients, the combination infusion time in hospital would be increased by 15-90 minutes and maintenance therapy would involve up to 15 extra hospital visits. In hospital, the same issues apply to bevacizumab as with other monoclonal antibodies. In approximately 18% of patients hypertension and therefore extra blood pressure monitoring/ management in the community may be required. At present there is no evidence to support re-treatment with bevacizumab at subsequent recurrences so that current opinion would favour administration of bevacizumab with a single regimen of treatment for a patient with ovarian cancer. The current available data makes it difficult to be certain for some patients whether to offer bevacizumab first-line or at relapse. However, the license is based on the two first-line randomised studies, both of which demonstrate a PFS advantage and one, ICON7, demonstrates an overall survival advantage, albeit at early analysis.

SUMMARY OF RECOMMENDATIONS OUTSIDE OF THIS SUBMISSION

In patients with platinum-sensitive recurrent ovarian cancer who have not received prior bevacizumab, this should be available to be administered with platinum-based chemotherapy regimens at 15mg/kg every 3 weeks during and after the chemotherapy until progressive disease occurs. In patients with platinum-resistant recurrent ovarian cancer who have not received bevacizumab previously, bevacizumab can be administered with cytotoxic regimens at 15mg/kg every 3 weeks until progressive disease occurs.

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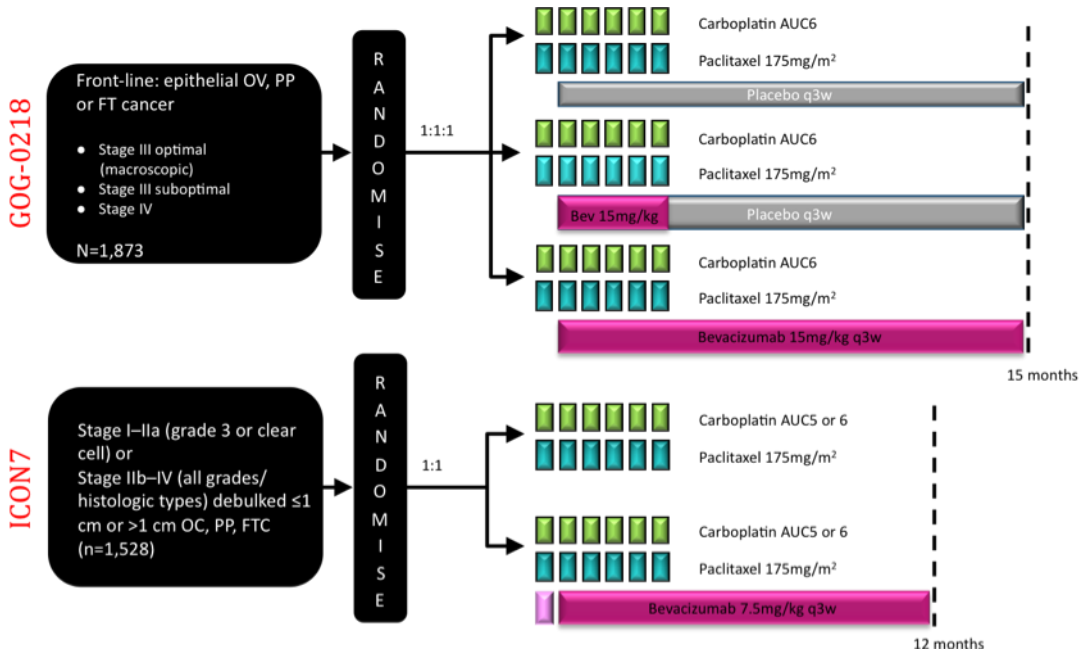
WHAT IS THE EXPECTED PLACE OF THE TECHNOLOGY IN CURRENT PRACTICE?

BACKGROUND

In the United Kingdom, the first line treatment of epithelial ovarian cancer (EOC) is surgery followed by carboplatin or carboplatin with paclitaxel[4], where the cytotoxic chemotherapy is administered on a 3-weekly basis for 6 cycles. Recent data have shown that delayed primary surgery in FIGO stage IIIc disease yields progression free- and overall survival statistics that equate with those obtained through the conventional approach where surgery occurs first[5]. Survival of advanced disease has remained poor for many years and new treatments are required.

RANDOMISED CLINICAL TRIALS OF BEVACIZUMAB IN 1ST LINE TREATMENT OF OVARIAN CANCER

Angiogenesis has been validated as a target in multiple randomised clinical trials that demonstrated improved progression free- or overall- survival in patients receiving conventional therapy supplemented with Vascular Endothelial Growth Factor (VEGF) inhibitors. In the first line treatment of ovarian cancer two randomised clinical trials, ICON7[6] and GOG218[7], have been conducted to evaluate the benefit for patients treated with carboplatin and paclitaxel when bevacizumab, an anti-VEGF antibody, is added. There are several important differences between the trials:



- **Patient characteristics**: ICON7 recruited 1528 patients with high-risk FIGO stage I-IIa (to a maximum of 10% i.e.152 patients) and all stage IIb-IV disease while GOG218 recruited 1873 patients initially with optimally (<1cm) and suboptimally debulked stage III disease and subsequently all stage III and IV disease. Thus in GOG218 approximately a third of patients had residual disease after surgery that was less than 1cm diameter. This is relevant as the implication

is that patients with any residual disease benefit from the addition of bevacizumab to cytotoxic therapy.

- **Design**: Both trials involved the administration of conventional doses of carboplatin and paclitaxel for 6 cycles. ICON7 had two non-blinded arms, where the experimental arm received bevacizumab 7.5mg/kg every 3 weeks for 12 months, starting from cycle 2 of the chemotherapy. GOG-218 was a placebo controlled, randomised trial where patients were randomised to one of three arms: conventional carboplatin and paclitaxel with placebo infusions; a second arm where carboplatin and paclitaxel were supplemented with bevacizumab for cycles 2-6, followed by placebo maintenance therapy for 15 months; and a third arm where patients received cytotoxic therapy with concurrent bevacizumab (cycles 2-6) followed by maintenance bevacizumab for 15 months from the initiation of treatment. The dose of bevacizumab in GOG218 was 15mg/kg every 3 weeks.
- **Data analysis and presentation**: the primary endpoints of both trials were PFS. Definition of progression in ICON7 was based on clinical assessment, Ca-125 and CT scans although patients were allowed to continue receiving bevacizumab if the only evidence of relapse was an elevated CA125, while the GOG218 trial defined progression according to radiological and biochemical data and bevacizumab was stopped on the basis of a rising CA125 alone as evidence of progressive disease. Here we will focus on the regulatory definitions of progression, which for both trials were based on CT scan-detected progression.
- **Key differences**: thus the key differences in the trials are: patient characteristics; blinded vs non-blinded trials; dose of bevacizumab; duration of maintenance phase of bevacizumab. Only the regulatory results will be discussed.

RESULTS AND SUBGROUP ANALYSIS

Mature progression free survival (PFS) data from both trials have been presented. In GOG218, the PFS in the control arm and combination/ maintenance arms were 12 and 18 months respectively (HR 0.63; $p<0.0001$). In ICON7, the PFS statistics in the control and combination/maintenance arms were 17.4 and 19.8 months, respectively ($p=0.87$; $p=0.039$). The differences in PFS in the two trials can be attributed to the variation in disease stage recruited to the trials; a pre-planned subgroup analysis of PFS in the 31% of ICON7 patients who had FIGO stage III/IV disease that exceeded 1cm diameter (high-risk subgroup -i.e. resembling 2/3 of GOG218 patient population) demonstrated PFS statistics of 10.5 and 16.0 months respectively (HR 0.68, $p<0.001$).

The data therefore show that the differences in PFS in the two trials between control and experimental arms with maintenance therapy, when the same stage and bulk of disease are considered, are the same; 6 months PFS advantage in GOG218 and 5.5 months in the ICON7 high-risk subgroup. Of note, however, is the fact that ICON7 (7.5mg/kg) used half the dose of bevacizumab used in GOG218 (15mg/kg).

Early overall survival (OS) statistics from ICON7[6] were reported following a regulatory request. Accepting the caveat that mature OS data will not be available for this trial until 2013, the data showed that there was no evidence of an OS benefit in low risk patients (early stage, well differentiated pathology and advanced disease

with optimal (<1cm) debulking), whereas those with stage III/IV, bulk residual disease (>1cm) incurred a median OS of 28.8 months in the control arm and 36.6 months in the experimental arm; a difference of approximately 8 months (HR 0.64; p=0.002). Immature OS data were reported for GOG218, although this was only ever a secondary endpoint in this trial. No difference in OS was observed. However, the high rate (40%) of crossover of patients from the control arm to receive bevacizumab is likely to explain this finding, and suggests that the impact of bevacizumab on OS cannot be determined accurately within the confines of GOG218.

The duration of maintenance therapy may be important. In the experimental arms (experimental arm ICON7 and arm III of GOG-218 where concomitant and maintenance therapy were given) patients received 12 months maintenance in ICON7 and 15 months in GOG218. Examination of the Kaplan-Meier survival curves suggests that the benefit of bevacizumab was lost once the drug was stopped; potentially suggesting that longer maintenance therapy would improve the PFS advantage. On the other hand, this is also the median time when progressive disease in stage III/IV ovarian cancer usually occurs. This point is likely to be answered with the results of the AGO-OVAR trial, BOOST, which randomises patients to 30 months of maintenance bevacizumab versus the 15 months utilised in GOG218 at the 15mg/kg dose.

In the second arm of GOG218, patients received bevacizumab only during the period of cytotoxic chemotherapy administration; there was no maintenance therapy component. However, in this group there was no improvement in PFS when compared with the control arm, implying that maintenance therapy is important and potentially challenging the role of the combination cytotoxic therapy-bevacizumab component of treatment.

Toxicities in GOG218 and ICON7

The toxicities observed in both trials are summarised in the table below. Some important points and caveats should be noted:

- In general, there is no evidence for a relationship between dose level and toxicity.
- The prevalence of gastro-intestinal toxicity in GOG218, which included perforation, fistula formation, necrosis and wound leak, was 2.5% during the chemotherapy-bevacizumab induction arm and 1% in the control population. However, in ICON7, which recorded bowel obstruction specifically, there was no difference in bowel perforation rates.
- Hypertension was assessed using different grades in the two trials; grade 3 in GOG218 and grade 2 in ICON7. Bearing that caveat in mind, the prevalence of hypertension (~18%) was the same in both trials.
- There is no explanation for the prevalence (12%) of grade 3 pain in the GOG218 trial
- There was a difference in the way that neutropenia was assessed in the two trials. In GOG218 interim blood counts were performed, whereas this was not the case in ICON7. Hence the apparent difference in neutropenia is most likely to be due to the measurement of nadir blood counts performed in GOG218.

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- Quality of life: data from ICON7 demonstrated that the quality of life of patients on both arms improved and that there was no significant differences between the arms. Quality of life data were not recorded in GOG218.

Select adverse events, % (grade when limited)	GOG-0218 CP		GOG-0218 CP + B15 → B15		ICON7 CP + B7.5 → B7.5
Patients, n	(n=601)	(n=483)	(n=608)	(n=464)	(n=745)
Cycles, n	2906	4059	2891	4677	
Treatment phase*	Cycles 2–6	Cycles 7–22	Cycles 2–6	Cycles 7–22	Overall
GI events‡ (grade ≥2)	1.0	<1.0	2.5	0.2	NR
Hypertension (grade ≥3)	3.5	4.5	9.9	17.0	18.3§
Proteinuria (grade ≥3)	0.3	0.4	0	2.2	0.5
Pain (grade ≥3)	21.1	25.5	18.4	37.5	NR
Neutropenia (grade ≥4)	57.4	0.4	63.3	0	16.5¶
Febrile neutropenia	3.5	0	4.3	0	2.8
Venous TE	4.3	1.9	4.4	3.0	6.7
Arterial TE	0.7	0.2	0.5	0.2	3.6
Wound-healing	1.8	1.2	2.1	1.1	5.0
CNS bleeding	0	0	0	0.4	NR
Non-CNS bleeding (grade ≥3)	0.5	0.4	1.6	0.6	1.2
RPLS	0	0	0	0.2	0

Table 1: Toxicities in GOG218 and ICON7
The toxicities are listed in the first column. In the second and third columns are the percent of patients who incurred that toxicity during the chemotherapy alone (white column 2) and during placebo maintenance therapy (grey column 3). In the 4th and 5th columns are the toxicities seen in the experimental arm of GOG218 during chemotherapy-bevacizumab treatment (white column 4) and during bevacizumab maintenance (grey column 5). The last column shows the toxicities in the experimental arm of ICON7. Note that the control arm was the same in both trials.
*onset within 30 days of last treatment. NR- not reported. ‡Perforation/fistula/necrosis/leak. §grade ≥2; ¶grade ≥3

Summary of ICON7 and GOG218 Data

In summary, the data from both trials show that patients with FIGO stage IIIc/IV ovarian cancer with any residual disease, whose carboplatin and paclitaxel therapy is supplemented with bevacizumab, attain a median improvement in PFS of 5.5-6 months. An early assessment of OS in ICON7 suggests that such 'sub-optimally debulked' patients treated with the cytotoxic-bevacizumab combination have improved overall survival. Maintenance therapy may be critical for this benefit but an optimum duration has not been established. In contrast, there is no evidence to support administration of bevacizumab to patients with FIGO stage I, II or IIIa disease. There remains debate about the definition of suboptimal resection. ICON7 had a cut-off of 1cm, while a third of patients in GOG218 had optimally resected disease suggesting that patients with any residual disease benefit from bevacizumab.

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OTHER FIRST-LINE TRIALS THAT MAY IMPACT ON USE OF BEVACIZUMAB

There are other trials that may subsequently influence decisions by NICE. These include the OCTAVIA study that tests the safety of the paclitaxel component, of the carboplatin-paclitaxel-bevacizumab (7.5mg/kg) combination, when given on a weekly or 3 weekly basis, an advance in paclitaxel therapy first described in a recent Japanese trial[8]. So far data from OCTAVIA have confirmed similar safety as both ICON7 and GOG218 but PFS / OS outcomes are awaited. The non-bevacizumab equivalent of the Japanese trial is MRC ICON8, which will provide further information on the role of weekly chemotherapy in the first line setting. GOG252 tests whether the platinum-paclitaxel regimen is more effective when the cytotoxic agents are administered through the intra-peritoneal route, as interest in this approach increased following a positive randomised trial in 2004[9]. AGO-OVAR12 evaluates the oral VEGF receptor tyrosine kinase inhibitor BIBF1120[10] with carboplatin and paclitaxel, while AGO-OVAR16 tests the role of pazopanib in the maintenance phase of treatment only. The results from these trials are not expected for at least another year.

OTHER TRIALS IN THE RECURRENT DISEASE SETTING

- **OCEANS**[11]: This is the first reported randomised trial that incorporated bevacizumab into second line treatment in the platinum-sensitive disease setting. Patients (n=484) with good performance status were randomly allocated to receive carboplatin and gemcitabine with placebo or bevacizumab. The trial had two unusual features including the possible extension of cytotoxic chemotherapy to ten cycles and the continued administration of bevacizumab 15mg/kg every 3 weeks until progression. The trial results have been presented recently and show that the control and experimental arms had a median PFS of 8.6 and 12.3 months, respectively (HR 0.45; p<0.0001). The OS data did not achieve pre-specified values of significance and demonstrate a trend to improved survival only (29.9 vs 35.5 months. HR 0.75; p=0.094). The PFS data are important as they demonstrate a 4-month improvement in PFS and a hazard ratio that is superior to that seen in GOG218 and the high-risk population in ICON7.
- **ICON6**: This randomised trial in platinum-sensitive disease tests the benefit of adding cediranib to carboplatin with gemcitabine/paclitaxel. The trial may well be affected by AstraZeneca's decision to halt development of cediranib
- **GOG213**: This randomised trial recruits patients with platinum sensitive recurrent disease and tests the benefit of adding bevacizumab to carboplatin and paclitaxel chemotherapy. It is also evaluates the effect of second look surgery and stratifies according to whether the patients have received previous bevacizumab.
- **AURELIA**[3]: This randomised trial tested the benefit of bevacizumab with physician's choice of chemotherapy in the platinum-resistant disease setting. 120 patients were randomised to receive cytotoxic chemotherapy (caelyx, weekly paclitaxel or topotecan) with or without bevacizumab 15mg/kg every 3 weeks until progressive disease occurred. Only 8% of patients had received previous bevacizumab. The primary endpoint was PFS, which was significantly improved from 3.4 to 6.7 months (HR 0.48; p<0.001). Overall survival data are not yet available and again may be confounded by a cross-over effect.

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CONCLUSION

- **Overall Survival**: Although the OS data for ICON7 have been published and demonstrate an early trend towards improved survival, mature OS data will only be available from 2013. However, it is on the basis of the significant extension of PFS in a very poor prognostic group (median overall survival of 29 months and PFS of 10 months) that bevacizumab should be made available for the first line treatment of women with good performance status who have FIGO stage IIIc/IV ovarian cancer with bulk residual disease.

IMPORTANT BUT UNRESOLVED QUESTIONS

The data from ICON7 and GOG218 provide us with guidance on the use of bevacizumab in the first line treatment of ovarian cancer, yet important issues remain unresolved. These include:

- **Dose Level of Bevacizumab**: ICON7 and GOG218 involved the administration of 7.5 mg/kg and 15 mg/kg every 3 weeks, respectively. Pre-planned subgroup analysis of high risk (suboptimally debulked) ovarian cancer patients in ICON7 demonstrated improvements in PFS and hazard ratio that correspond closely with the overall data from GOG218 suggesting that the two dose levels are equally effective. By virtue of the superior placebo-controlled design of the GOG trial, and the absence of timely data from the MRC ICON7 trial, the data and dose from GOG218 were chosen to present to the licensing authorities, together with supportive data from ICON 7. However, it is important to note that a third of the patients recruited to the GOG218 trial had 'optimally debulked' (<1cm residual disease) patients while two thirds had disease that resembled the high risk group in ICON7 (suboptimally debulked).
- **Duration of Maintenance Therapy**: Pre-clinical data and the observed loss of benefit from bevacizumab upon discontinuation in both trials suggest that maintenance therapy should be continued until progression for women with any residual disease. However, 20% of patients with FIGO stage III disease will be cured by conventional surgery and cytotoxic treatment, in which case it would be unclear when to stop maintenance therapy. As the maximum duration of treatment assessed so far is 15 months therefore the recommendation for women with a radiological and biochemical CR would be for up to 15 months bevacizumab . Research to assess the optimum duration of maintenance therapy is ongoing.
- **Neoadjuvant (Pre-Operative) Chemotherapy**: Neither ICON7 nor GOG218 recruited patients for pre-operative chemotherapy with planned delayed surgery. While pre-operative chemotherapy has been widely implemented in the UK there are no published data concerning the incorporation of bevacizumab into pre-operatively treated patients. However, the equivalence of pre-operative and conventional chemotherapy approaches has been demonstrated in ovarian cancer and both GOG218 and ICON7 show that bevacizumab can be administered safely providing it is withheld 6 weeks before and after surgery. Additional evidence comes from trials of bevacizumab in other tumour types (oesophagus and stomach cancers, STO3), which incorporate interval surgery without incurring excess adverse events. Given, these data, it seems appropriate to administer bevacizumab with platinum-containing therapy in the neoadjuvant setting at 7.5mg/kg every 3 weeks for up to 15 months from the start of treatment.

Bevacizumab should be omitted from the dose of cytotoxic chemotherapy given before and after surgery.

- **Carboplatin and Bevacizumab**: ICON3 demonstrated the activity of carboplatin in the first line treatment of all stages of ovarian cancer[4]. However, both GOG218 and ICON7 used carboplatin and paclitaxel as the cytotoxic components. Although investigators could continue therapy with carboplatin if paclitaxel was withdrawn (e.g. through allergy or neuropathy), prospective data on the safety, efficacy and quality of life of carboplatin and bevacizumab combinations would be helpful.
- **Patients Who Attain a Biochemical and Radiological Complete Response**: The data from ICON7 suggest that patients with low risk (ie low stage and grade) ovarian cancer do not benefit from bevacizumab. Therefore, it will be important to examine the benefit from bevacizumab in patients with FIGO stage III/IV disease who attain a biochemical and radiological complete response from remission-induction therapy. Is maintenance therapy effective in patients with no residual disease at the end of remission induction therapy for stage III/IV disease? Evaluation of the differential PFS benefit from bevacizumab in patients with a complete vs partial response at the end of the chemotherapy-bevacizumab combination should be performed on the ICON7 and GOG218 data.
- **Predictive biomarkers**: Despite a global effort involving thousands of patients there has been no predictive biomarker until very recently. A new assay that measures soluble, low molecular weight VEGF-A isoforms was of predictive value in the retrospective evaluation of breast, pancreatic and gastric cancer specimens[12]. Prospective evaluations in breast and lung cancer are under way. However, no data are available with ovarian cancer and research in this area is urgently required.
- **Fertility preserving therapy**: It is unlikely that bevacizumab will be used in fertile women with early stage ovarian cancer, who are undergoing fertility sparing surgery and chemotherapy. However, VEGF inhibitors are potent suppressors of ovarian follicular and corpus luteum function and the effect of bevacizumab on long term ovarian function is not known. It would therefore be inappropriate to administer bevacizumab in this scenario. However, ongoing audit of such cases would be important.
- **Poor Performance Status Patients and Contra-indications to Bevacizumab**: Neither ICON7, GOG218 nor OCEANS recruited patients with poor performance status. The risk of bowel perforation in these patients is likely to be increased, particularly in those with bulk disease and symptoms of bowel obstruction. However, as VEGF inhibitors are active in patients with ascites research in this group of patients should also be pursued.
- **Retreatment**: Four randomised trials have demonstrated an improved PFS in patients with ovarian cancer who are receiving first line (GOG218 and ICON7); platinum sensitive recurrent ovarian cancer (OCEANS) and platinum resistant ovarian cancer (AURELIA). These trials have largely or completely omitted patients who have received bevacizumab previously. Therefore at present there is no clinical evidence to show that re-treatment with bevacizumab is appropriate. There is an on-going trial (bevacizumab beyond progression, BBP) running in Europe (MITO / MANGO) which will answer this question, hopefully in 2016.

However, from the experimental point of view it is likely that the vasculature will remain a valid target in ovarian cancer.

NHS IMPLICATIONS

Provision of bevacizumab in the first line setting for patients with bulk-residual FIGO stage III/IV disease, would involve treatment of approximately 3200 patients. This is based on the assumption that of the 7000 patients who develop ovarian cancer each year in the UK, 70% will have FIGO stage III/IV disease i.e. 4900 patients. Of these, approximately 25% will have surgery that achieves optimal debulking (no residual disease and therefore no indication for bevacizumab) and another 10% will be too unwell or have other contraindications to bevacizumab. Thus 3185 patients would be eligible for treatment with carboplatin, paclitaxel and bevacizumab in the first line setting each year.

The impact on the NHS would be that chemotherapy administration time would increase from 5 to 5.5-6.5 hours (bevacizumab is given over 1.5 hours for the first infusion and if tolerated, subsequent infusions can be administered over 30 minutes from the 3rd infusion. Patients would receive approximately up to 15 months maintenance therapy. Given a 3-weekly cycle this would mean an extra 11 to 15 hospital visits and infusions of bevacizumab, over 30-90 minutes.

Community medical input would be required to support the monitoring and management of hypertension in the 18% who will develop this as a consequence of bevacizumab. Data from GOG218 suggests that the prevalence of hypertension during maintenance bevacizumab exceeds that in the combination cytotoxic and bevacizumab arm; thereby mandating ongoing review of hypertension during the entire period that the patient receives bevacizumab. Otherwise, the administration of bevacizumab is associated with the same issues as other monoclonal antibodies already implemented e.g. trastuzumab.

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