AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Bevacizumab at a dose of 7.5 mg/kg in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression (OW01)

September 2021

ONE WALES INTERIM DECISION

Bevacizumab 7.5 mg/kg dose in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression

Date of original advice: June 2017
Date of review: September 2021

The following One Wales Assessment Group (OWMAG) recommendation has been endorsed by health board Chief Executives.

Bevacizumab 7.5 mg/kg dose in combination with carboplatin and paclitaxel can continue to be made available within NHS Wales for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression. High risk is defined as: International Federation of Gynaecology and Obstetrics [FIGO] stage III debulked but residual disease more than 1.0 cm or stage IV disease, or stage III disease at presentation and requiring neoadjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction.

Bevacizumab 7.5mg/kg dose is not licensed to treat this indication and is therefore 'off-label'. Each provider organisation must ensure all internal governance arrangements are completed before these medicines are prescribed in combination.

The risks and benefits of the off-label use of bevacizumab for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice assists consistency of access across NHS Wales and will be disseminated to the service following agreement of Health Board Chief Executives.

Starting and stopping criteria for bevacizumab at a dose of 7.5 mg/kg in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression

Prescribers should note that front-line treatment with bevacizumab is now available for patients with stage III and IV homologous recombination deficiency (HRD)-positive disease who are eligible to receive olaparib plus bevacizumab maintenance therapy in line with the National Institute for Health and Care Excellence (NICE) guidance TA693 and should refer to this for full eligibility criteria[1].

These criteria are adapted from the NHS England National Cancer Drugs Fund List[2].

Starting criteria:

Patients with newly diagnosed epithelial ovarian, fallopian tube or primary peritoneal cancer with sufficient performance status to undergo treatment with carboplatin, paclitaxel and bevacizumab in one of the following groups:

- patients with FIGO stage III debulked but residual disease more than 1 cm
- patients with stage IV disease
- patients with stage III disease at presentation and requiring neoadjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction.

Patients who satisfy the eligibility criteria will be prescribed bevacizumab following consultation with the patient and/or carer taking into account potential adverse effects, cautions and contraindications. This consultation should be recorded in the patient's notes.

Bevacizumab is prescribed at a dose of 7.5 mg/kg every three weeks up to a maximum of 18 cycles. Bevacizumab should be given with the:

- first or second cycle of chemotherapy following primary debulking surgery or for those patients with stage IV disease or inoperable disease or who are unable to undergo surgery due to increased risk during COVID19
- first or second cycle of chemotherapy following interval debulking surgery performed after three to four cycles of neoadjuvant chemotherapy
- first or second cycle of neoadjuvant chemotherapy.

Stopping criteria:

- radiological or clinical evidence of disease progression
- toxicity
- patient request
- after 18 cycles of bevacizumab.

References

1. National Institute for Health and Care Excellence. Technology Appraisal TA693. April 2021. Available at: https://www.nice.org.uk/guidance/ta693. Accessed August 2021.
2. NHS England. National Cancer Drugs Fund. July 2021. Available at: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/. Accessed August 2021.

This is a summary of new evidence available and patient outcome data collected, to inform the review

Background
Ovarian cancer is the leading cause of death from gynaecological cancer in the UK[1]. The outcome for women with ovarian cancer is generally poor, with an overall five-year survival rate in Wales of 47.8%[2]. Women with advanced ovarian cancer (FIGO stage III or IV) have a five-year survival rate of 24.9% and 6.5 %, respectively[2]. Bevacizumab 7.5 mg/kg dose was on the Cancer Drugs Fund in England for patients with FIGO stage III debulked but residual disease more than 1.0 cm or stage IV disease, or stage III disease at presentation and requiring neoadjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction[3]. A cohort of patients was identified in Wales based on data from individual patient funding request panels. Clinicians in Wales considered there to be an unmet need and based on these two factors this medicine was considered suitable for assessment via the One Wales process.

Current One Wales decision
Bevacizumab 7.5 mg/kg dose in combination with carboplatin and paclitaxel can be made available within NHS Wales for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression. High risk is defined as: International Federation of Gynaecology and Obstetrics [FIGO] stage III debulked but residual disease more than 1.0 cm or stage IV disease, or stage III disease at presentation and requiring neoadjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction[4]. Reviewed in September 2020.

Licence status
Bevacizumab 7.5 mg/kg dose in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression is off label.

Guidelines
An eUpdate to the European Society for Medical Oncology (ESMO) clinical practice guideline Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma was issued in July 2021. This includes the recommendation that patients with a positive homologous recombination deficiency (HRD) test and a partial or complete response to front-line platinum-based chemotherapy, with or without bevacizumab, should receive maintenance treatment with a PARP inhibitor, either olaparib/bevacizumab (if started with chemotherapy) or niraparib monotherapy[5].

Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines
Bevacizumab is available through NHS England clinical policy for first line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression[3].

NICE TA693 published in April 2021 recommends olaparib plus bevacizumab for use within the Cancer Drugs Fund as an option for maintenance treatment of advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults when:

- there has been a complete or partial response after first-line platinum-based chemotherapy plus bevacizumab, and
- the cancer is associated with HRD positive status defined by mutations in either BRCA1 or BRCA2 tumour suppressor genes and/or genomic instability[6].

Implementing the above recommendation required changes to be made to the first-line treatment pathway. Specifically, all patients with stage III and IV HRD-positive disease would have to be offered first-line bevacizumab plus platinum-based chemotherapy[6]. Hence, bevacizumab at its licensed dose of 15 mg/kg is listed on the Cancer Drugs Fund, through NHS England clinical policy, in addition to the off-label 7.5 mg/kg dose for use in combination with platinum-based chemotherapy as induction therapy for up to six cycles[3]. Eligible patients may then go on to receive olaparib plus bevacizumab (15 mg/kg) as maintenance treatment. Patients who have not received bevacizumab as induction therapy but have stage III-IV HRD-positive disease are also eligible to receive olaparib plus bevacizumab maintenance therapy.

For those patients not eligible to receive olaparib, the option for patients who have received bevacizumab 7.5 mg/kg as induction therapy to continue to receive bevacizumab 7.5 mg/kg monotherapy for up to 18 cycles in total is retained[3].

Efficacy/effectiveness
No new relevant clinical effectiveness evidence was identified in the repeat literature search.

Safety
No relevant safety analyses were identified in the repeat literature search.

Cost effectiveness
No relevant cost-effectiveness analyses were identified in the repeat literature search.

Budget impact
Three biosimilar bevacizumab preparations are now available in the UK[7-9]. The list price for these biosimilars is 2–15% lower than the cost of the reference medicine, Avastin®[10]. This, however, does not take in to account any current or future contract prices which may be significantly different to the list prices for the reference product and the biosimilars.

Following the additions made to the Cancer Drugs Fund it is likely that the number of patients requiring access to bevacizumab 7.5 mg/kg via the One Wales Interim Decision route may decrease.

Impact on health and social care services
The impact on the service remains minimal.

Patient outcome data
At the time the review was considered by OWMAG, no patient outcome data had been received. Subsequent data received indicates that the patient numbers, treatment cycles and rate of disease progression are comparable to evidence previously presented.

References

1. National Institute for Health and Care Excellence. Quality Standard 18. Ovarian cancer. May 2012. Available at: http://www.nice.org.uk/guidance/qs18. Accessed August 2021.
2. Welsh Cancer Intelligence and Surveillance Unit. Cancer survival in Wales 1995-2016. July 2019. Available at: https://phw.nhs.wales/services-and-teams/welsh-cancer-intelligence-and-surveillance-unit-wcisu/cancer-survival-in-wales-1995-2016/. Accessed August 2021.
3. NHS England. National Cancer Drugs Fund. July 2021. Available at: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/. Accessed August 2021.
4. All Wales Therapeutics and Toxicology Centre. One Wales Interim Decision: Bevacizumab (Avastin®) at a dose of 7.5 mg/kg in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. July 2019. Available at: https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/one-wales-bevacizumab-avastin-for-ovarian-cancer/. Accessed August 2021.
5. Colombo N and Ledermann JA. eUpdate - Updated treatment recommendations for newly diagnosed epithelial ovarian carcinoma from the ESMO Clinical Practice Guidelines. July 2021. Available at: https://www.esmo.org/guidelines/gynaecological-cancers/newly-diagnosed-and-relapsed-epithelial-ovarian-carcinoma/eupdate-newly-diagnosed-epithelial-ovarian-carcinoma-treatment-recommendations. Accessed August 2021.
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7. Zentiva. Alymsys®. Summary of Product Characteristics. April 2021. Available at: https://www.medicines.org.uk/emc/product/12588/smpc. Accessed August 2021.
8. Organon Pharma (UK) Limited. Aybintio®. Summary of Product Characteristics. January 2021. Available at: https://www.medicines.org.uk/emc/product/11801/smpc. Accessed August 2021.
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10. British National Formulary. Bevacizumab: Medicinal Forms. Available at: https://bnf.nice.org.uk/medicinal-forms/bevacizumab.html. Accessed August 2021