Olaparib and Bevacizumab

Indication

Maintenance treatment of advanced (stage III or IV) predominantly high grade serous, endometrial or clear cell carcinoma of ovary, fallopian tube or primary peritoneum, after response to first line platinum based chemotherapy in patients who are Homologous recombination deficiency (HRD) positive

- HRD positive defined by either deleterious / suspected deleterious BRCA1 and/or BRCA2 mutation, or genomic instability as defined by a score of > or = to 42 by the Myriad HRD test
- Must have had a minimum of 4 cycles of platinum based chemotherapy. Olaparib must be started within 9 weeks of the last infusion of the last cycle of chemotherapy. Bevacizumab can be started at the same time as olaparib or alongside the chemotherapy
- Must be in response to 1st line treatment defined as a partial or complete response to treatment and no progressive disease on a post-treatment CT scan or rising CA125

Regimen details

Olaparib tablets 300mg twice daily orally (with or without food). Given continuously (on a 21 day cycle to fit with the bevacizumab)

Bevacizumab 15mg/kg intravenously in 100ml 0.9% sodium chloride, every 3 weeks

Cycle frequency

Every 3 weeks (olaparib can be given monthly when not given with bevacizumab)

Number of cycles

Olaparib to continue until disease progression, unacceptable toxicity or for a **maximum of 2 years** (whichever is sooner)

Bevacizumab to continue until disease progression, unacceptable toxicity or for a maximum of **15 months** measured from the 1st treatment whether this is given with chemotherapy or started after chemotherapy (whichever is sooner)

Delays and Treatment breaks:

Bevacizumab is limited to 15 months and olaparib is limited to 2 years regardless of delays or breaks in treatment.

Administration

Bevacizumab:

1st dose given over 90 minutes, 2nd dose over 60 minutes and subsequent doses can be given over 30 minutes if tolerated. If infusion reaction of grade 2 or less at 90 min infusion give next with paracetamol and chlorphenamine premedication and continue at 90 mins (if well tolerated can then reduce infusion rate in future but continue premedication). If infusion reaction of grade 2 or less during 60 minute infusion increase to 90 min with premedication. If infusion reaction more severe than grade 2 discontinue permanently

Olaparib:

Tablets should be swallowed whole (with or without food) and not chewed, crushed, dissolved or divided. If a patient misses a dose, the next dose should be taken at the next scheduled time.

Pre-medication

None

Emetogenicity

Minimal (no routine antiemetics required)

Additional supportive medication

None

Extravasation

Neutral

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
HRD status	Baseline
CT scan	Post chemotherapy
BP	Baseline
Urine dipstick for proteinuria	Baseline

Any pre-existing hypertension must be controlled prior to starting bevacizumab

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating bevacizumab, this risk should be carefully considered in patients with risk factors such as hypertension, history of aneurysm, or dissection

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), blood pressure, urine dipstick for proteinuria

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 50 mL/min
Bilirubin	≤ 1.5 x ULN
AST	< 1.5 x ULN
Blood pressure	<140/90 mmHg

Delay 1 week if above parameters not met. If not recovered after 1 week contact consultant for clinic review and dose reduction

Dose modifications

Olaparib:

Olaparib can be administered at full dose in mild renal impairment (CrCl >50)
In moderate renal impairment (CrCl 31-50ml/min) reduce olaparib dose to 200mg twice daily
Not recommended in patients with hepatic impairment (bilirubin >1.5 x ULN)
Avoid co-administration with strong CYP3A inducers or inhibitors
If a strong or moderate CYP3A inhibitor must be co-administered, the dose of olaparib should be reduced

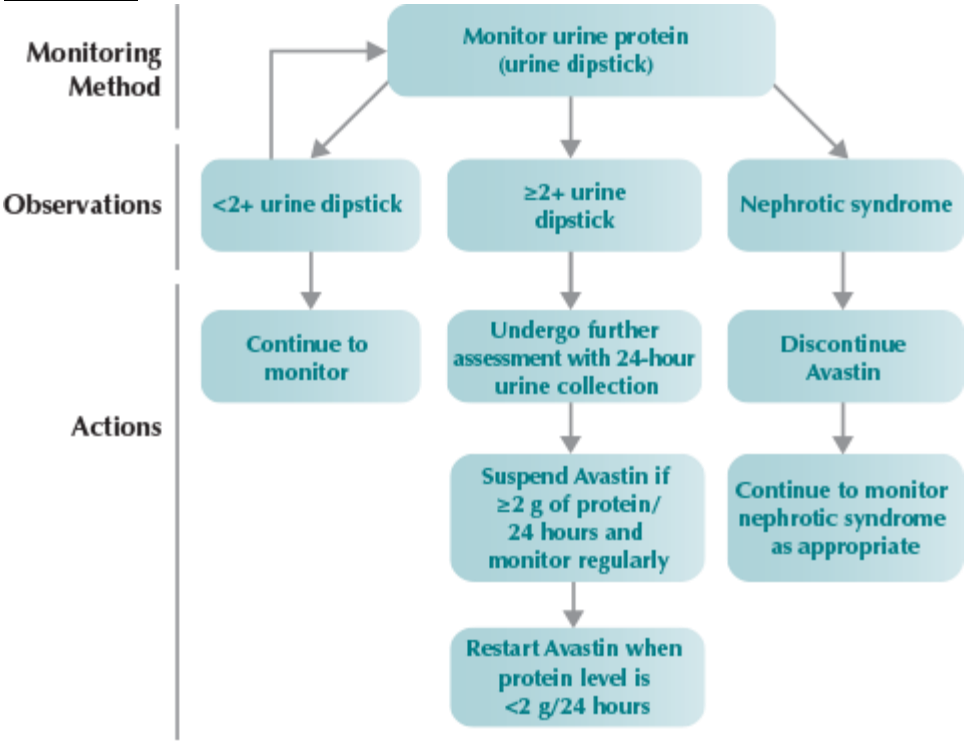
Bevacizumab:

Do not reduce the dose of bevacizumab. Dosing should be interrupted or discontinued as described below

Toxicity	Grade	Dose adjustment
Infusion related reactions	Grade ≤2	90 minute infusion: continue with dose as normal, but give premedication (paracetamol and chlorphenamine) with the next

		dose and give over 90 minutes. If well tolerated subsequent infusions can be reduced by 30 minutes as long as use premedication.
		60 minute infusion: all subsequent doses should be given over 90 minutes (with pre-medication)
		30 minute infusion: all subsequent doses should be given over 60 minutes (with pre-medication)
	Grade ≥2	Discontinue permanently
Proteinuria (on dipstick)	<2	Continue with bevacizumab as normal
	≥2+	See algorithm below
	Nephrotic syndrome	Permanently discontinue
Gastro-intestinal perforation or dehiscence		Discontinue permanently
Wound healing complications		Bevacizumab should not be initiated for at least 28 days following surgery or until wound is fully healed Bevacizumab should be withheld for 42 days (6 weeks) prior to elective surgery If would healing complications occur during treatment it should be withheld until the wound is fully healed.
Fistula or intra-abdominal abscess		Discontinue permanently
Venous thromboembolic event	Grade 3 Deep DVT or cardiac thrombosis needing anticoagulation or incidental first PE	Hold bevacizumab for 2 weeks May be resumed after initiation of therapeutic dose anticoagulant
	Grade 4 Embolic event including PE with life-threatening thrombus	Discontinue permanently
Arterial thrombotic event	ANY grade	Permanently discontinue
Haemorrhage	Grade 1 or 2	No modification but institute appropriate treatment
	Grade 3 or 4	Discontinue and institute appropriate treatment

Proteinuria



Hypertension

	Definition	**Action**
Grade 1	Asymptomatic transient (<24 hours) increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously normal.	Recheck BP 1 hour later If BP <140/90 mmHg: administer as normal If BP 140/90-150/100 mmHg administer but recheck BP 48 hours later If >150/100 mmHg omit bevacizumab and recheck BP 48 hours later If BP after 48 hours still >140/90 mmHg commence antihypertensive therapy
Grade 2	Recurrent or persistent (>24 hour) increase by 20 mmHg (diastolic) or to >140/90 mmHg if previously normal	Anti-hypertensive therapy should be commenced. Once controlled to <140/90 mmHg bevacizumab can be continued
Grade 3	Requiring more than one antihypertensive or more intensive therapy than previously	Withhold bevacizumab for persistent hypertension >140/90 mmHg If hypertension cannot be controlled, discontinue permanently
Grade 4	Life threatening (hypertensive crisis)	Medical emergency Permanently discontinue

Wound healing – Bevacizumab should not be initiated for at least 28 days following surgery or until wound is fully healed. It should be withheld for 42 days (6 weeks) prior to any elective surgery. In the event of any wound healing complications it should be withheld until the wound is fully healed.

Permanent discontinuation in the event of a fistula or intra-abdominal abscess

VTE

If uncomplicated DVT /PE, hold bevacizumab for 2 weeks and anticoagulated, bevacizumab can then be continued.
Permanently discontinue for arterial thrombotic event

Pneumonitis
Fatal pneumonitis has been reported in patients taking olaparib. If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib should be discontinued.

Adverse effects –

for full details consult product literature/ reference texts

Olaparib:
Reduced appetite, Altered taste, Headache, Dizziness, Nausea, Vomiting, Diarrhoea, Dyspepsia, Stomatitis, Upper abdominal pain, Fatigue, Anaemia, Neutropenia, Thrombocytopenia
Myelodysplastic syndrome / Acute Myeloid Leukaemia <1.5%
Pneumonitis (including events with a fatal outcome) have been reported in <1.0%

Bevacizumab:
Hypertension, Proteinuria, Fistulae and perforations, wound healing complications, Posterior reversible encephalopathy syndrome (PRES), Arterial thromboembolism, Venous thromboembolism, Haemorrhage, Aneurysms and artery dissections, Congestive heart failure, Neutropenia and infections, Hypersensitivity and infusion reactions

Significant drug interactions

– for full details consult product literature/ reference texts

Strong or moderate CYP3A inhibitors: (e.g. itraconazole, telithromycin, clarithromycin, erythromycin, diltiazem, fluconazole, verapamil) co-administration is not recommended. If a strong or moderate CYP3A inhibitor must be co-administered, the dose of olaparib should be reduced. See SPC for further information.

Strong or moderate CYP3A inducers: (e.g. phenytoin, rifampicin, carbamazepine, nevirapine, phenobarbital, St John's Wort, efavirenz, rifabutin) co-administration is not recommended. If a patient already receiving olaparib requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of olaparib may be substantially reduced. See SPC for further information.

Sensitive CYP3A substrates or substrates with a narrow therapeutic margin: (e.g. simvastatin, cisapride, cyclosporin, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine) use with caution and close clinical monitoring. Hormonal contraceptives: efficacy may be reduced, use alternative forms of contraception.

Substrates of P-gp: (e.g. simvastatin, pravastatin, dabigatran, digoxin and colchicine) use with caution and close clinical monitoring.

In vitro, olaparib has been shown to be an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K

Additional comments

Olaparib tablets and capsules are not interchangeable. This protocol is for olaparib tablets only.

References

Lynparza SPC - https://www.medicines.org.uk/emc/product/9204/smpc

Avastin SPC - https://www.medicines.org.uk/emc/product/3885

PAOLO 1 study - https://www.nejm.org/doi/full/10.1056/NEJMoa1911361

THIS PROTOCOL HAS BEEN DIRECTED BY DR MOON, CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

Date: