Retifanlimab Carboplatin Paclitaxel

Indication
Treatment of inoperable locally recurrent or metastatic squamous anal cancer

Regimen details

Day	Drug	Dose	Route
1	Retifanlimab	500mg	IV Infusion
1, 8, 15	Paclitaxel	80mg/m^2	IV infusion
1	Carboplatin	AUC5	IV infusion

(Maximum carboplatin dose 790mg)

Cycle frequency
28 days

Number of cycles
Retifanlimab given in combination with carboplatin and paclitaxel for up to 6 cycles.
Continue retifanlimab maintenance for maximum 13 cycles in total.

Administration
Retifanlimab is given before paclitaxel and carboplatin
Retifanlimab is administered over 30 minutes in 100ml 0.9% sodium chloride using a 0.2micrometre filter.

Paclitaxel should be administered before carboplatin. Paclitaxel should be administered in 250mls of 0.9% sodium chloride IV over 1 hour. Carboplatin should be administered in 500mls of 5% Glucose IV over 30-60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of paclitaxel or carboplatin. Facilities for the treatment of hypotension and bronchospasm must be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve restarted at a slower infusion rate. Chlorphenamine 10mg IV may be administered. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of paclitaxel or carboplatin and appropriate therapy should be initiated.

See table on page 4 for management of retifanlimab infusion reactions

Pre-medication
30 minutes prior to each paclitaxel infusion:
Chlorpheniramine 10mg IV slow bolus
Dexamethasone 10mg IV slow bolus
Famotidine 20mg oral (or alternative H_2 antagonist)

For subsequent weeks reduce dexamethasone dose to 8mg then 4mg then stop dexamethasone. If patient experiences any hypersensitivity reaction do not reduce the dose further but continue with the same or increased dose of dexamethasone. If severe reaction, change regimen/ remove offending agent.

Continue to give dexamethasone 8mg as anti-emetic pre-med for carboplatin day 1.

Stop H_2 antagonist after 3 doses if paclitaxel tolerated

Emetogenicity

This regimen has moderate emetic potential on day 1 and low emetic potential on days 8 & 15

Additional supportive medication

Proton pump inhibitor if required
Loperamide if required
Mouthwashes as per local policy

Extravasation

Carboplatin - irritant (group 3)
Paclitaxel - vesicant (group 5)
Retifanlimab - neutral (group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs (including AST)	14 days
Bone profile	14 days
Hepatitis B serology (HBsAG, HBcAb)	none
HIV serology	none
HbA1c	3 months
Random glucose	14 days
Calculated creatinine clearance	14 days
ECG	28 days
Troponin T	14 days
Pro BNP	14 days
Creatine Kinase	14 days
Cortisol	14 days
Amylase	14 days
Thyroid Function	14 days

Consider baseline measured GFR if suspected or significant renal dysfunction

Investigations –pre subsequent cycles

Day 1 Troponin, ProBNP, Creatine Kinase, Cortisol
Day 1,8 and 15
FBC, U+E (including creatinine), LFT (including AST), Calcium, Magnesium, glucose

Thyroid Function 6-8 weekly

Standard limits for administration to go ahead

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

- **Immunotherapy related toxicities**

Immunotherapy toxicities should be aggressively managed as can cause permanent and life-threatening complications. Refer to UKONS and ESMO guidance for treatment of immune related toxicities. Available at: https://www.lancashireandsouthcumbria.icb.nhs.uk/our-work/canceralliance/information-professionals/clinical-reference-groups/chemotherapy-crg

Investigation	Limit
Neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 30 mL/min (and <10% change)
Bilirubin	≤ 1.5 x ULN
AST or ALT	< 5 x ULN

Day 8 + Day 15
Proceed if blood results below within range otherwise omit dose.

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 75 x 10^9/L

Dose modifications

Dose levels

	Paclitaxel	Carboplatin
Starting dose	80mg/m^2	AUC5
Dose level -1	70mg/m^2	AUC4
Dose level -2	60mg/m^2	AUC3.5

- ### Haematological toxicity

Day 1

Neutrophils (x10^9/l)		Platelets (x10^9/l)	Carboplatin dose (day 1)	Paclitaxel dose (day 1)
≥ 1.5	and	≥100	100%	100%
≤1.5	or	<100	Delay 1 week (or until recovery) then reduce dose by 1 dose level	Delay 1 week (or until recovery)
≤1.5	and	<100	Delay 1 week (or until recovery) then reduce dose by 1 dose level	Delay 1 week (or until recovery) then reduce all future doses by 1 dose level

If haematological toxicity causing omission of a paclitaxel dose (day 8 or day 15) - no dose modification is required.
If omission of both paclitaxel administrations (day 8 and day 15) doses of carboplatin and paclitaxel should be modified according to the day 8 or 15 blood count as per the table above.

In the case of febrile neutropenia (neutrophils < 0.5 × 10^9 /L and fever > 38.5°C requiring IV antibiotics) reduce paclitaxel to 60mg/m^2 and carboplatin by 1 x AUC for all subsequent doses.

- ### Hepatic Impairment

Paclitaxel: Paclitaxel is not recommended in severe hepatic impairment. If bilirubin < 1.5 x ULN and AST/ALT < 5 x ULN proceed with 100% dose.
For more severe hepatic impairment, treatment may only proceed on consultant's decision, at a reduced dose with weekly monitoring of LFTs.

Carboplatin: Transient increases in liver enzymes have been seen in patients being treated with carboplatin although no dose reduction is usually required. If bilirubin ≥ 3 x ULN and/or transaminases ≥ 5 x ULN discuss with consultant.

- ### Renal impairment

If calculated CrCl falls by >10% from previous dose, consider measured GFR and / or dose recalculation.

CrCl (mL/min)	Carboplatin dose
>30	100%
20-30	Measured GFR then 100%. Consider alternative non-nephrotoxic regimen
<20	Contra-indicated

- ### Other toxicities

Toxicity	Definition	Carboplatin dose	Paclitaxel dose
Neuropathy	Grade 2	100%	Paclitaxel to be withheld until resolved to grade 1. Restart at a reduction of 1 dose level. If >2 week delay required, omit Paclitaxel from ongoing cycles.
	Grade 3-4		Paclitaxel should be omitted from subsequent cycles
Mucositis	Grade 2	100%	Delay until resolved to grade 1. No dose reduction required.
	Grade 3		Delay until resolved to grade 1. Dose reduce paclitaxel by one dose level in subsequent cycles. If mucositis persists at grade 3 for more than two weeks or recurs despite dose reduction, then paclitaxel should be omitted from subsequent cycles.
Fatigue	Grade 3	100%	1st occurrence – reduce by one dose level for all subsequent doses or omit.
Arthralgia/ Myalgia	Grade ≥2	100%	Consider diclofenac +/- co-codamol or prednisolone 10mg BD for 5 days starting 24 hours post paclitaxel. If persists reduce dose by one dose level

For any grade 3 non-haematological toxicity, withhold until symptoms resolve to grade 1. On recovery, the causative chemotherapy agent should be reduced by 1 dose level in subsequent cycles.

For any grade 4 toxicity (except alopecia and nausea and vomiting) withhold and discuss with consultant.

- **Retifanlimab Infusion Reactions**

Grade	Description	Treatment	Subsequent Infusions
1	Mild reaction; infusion interruption not indicated; intervention not indicated.	Monitor vital signs closely until medically stable.	Premedication with an antipyretic (e.g. acetaminophen/paracetamol) and a histamine blocker (e.g. diphenhydramine) should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.
2	Requires infusion interruption but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	First occurrence: Stop infusion and initiate appropriate medical measures (e.g. IV fluids, antihistamines NSAIDS, paracetamol, narcotics, per institutional preferences). Monitor vital signs until medically stable. If symptoms resolve within 1 hour, infusion may be resumed at 50% of the original infusion rate. Subsequent occurrences (after recommended prophylaxis): Permanently discontinue treatment.	Premedicate at least 30 minutes before infusion with antihistamines (e.g. chlorphenamine 10mg IV) and paracetamol (500-1000 mg PO). Additional supportive measures may be acceptable (per institutional preference). Next infusion should start at 50% of the original infusion rate. If no reaction, the rate of infusion can be increased by 25% every 15 minutes until a rate of 100% has been reached. Subsequent infusions can begin at 100%.

3 or 4	**Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltrates). **Grade 4:** Life-threatening; vasopressor or ventilatory support indicated.	Stop infusion and initiate appropriate medical therapy (e.g. IV fluids, antihistamines NSAIDS, paracetamol, narcotics, oxygen, vasopressors, epinephrine, corticosteroids, per institutional preferences). Monitor vital signs frequently until they are medically stable. Hospitalization may be indicated.	Permanently discontinue treatment.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Teratogenicity
Hypersensitivity reactions
Pulmonary fibrosis
Nephrotoxicity
Electrolyte disturbances
Arrhythmias
Cardiac failure

- **Frequently occurring side effects**

Nausea and vomiting
Mucositis, stomatitis
Myelosuppression
Diarrhoea, constipation
Peripheral neuropathy
Oedema
Phlebitis
Myalgia, arthralgia
Alopecia
Fatigue

- **Other side effects**

Flu-like symptoms
Taste changes
Headache
Abdominal pain
Deranged liver function

Elderly patients may have a higher incidence of severe neuropathy, severe myelosuppression, or cardiovascular events compared to younger patients.

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.
Clozapine: increased risk of agranulocytosis
Paclitaxel is a CYP 2C8 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Carboplatin only: Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use
Diuretics: increased risk of nephrotoxicity and ototoxicity Nephrotoxic drugs: increased nephrotoxicity; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin

Additional comments

Carboplatin dose calculated using the Calvert equation: Carboplatin dose (mg) = AUC (CrCl +25)

Measured GFR (such as 24-hour urine or 51Cr-EDTA) is preferred whenever feasible, particularly in circumstances of co-morbidity that could affect renal function such as dehydration or extremes of weight. Alternatively, the Cockcroft and Gault Method can also be used to estimate a patient's CrCl.

References

- Summary of Product Characteristics Paclitaxel accessed via www.medicines.org.uk on 20th September 2024
- Summary of Product Characteristics Carboplatin accessed via www.medicines.org.uk on 20th September 2024
- Retifanlimab with carboplatin and paclitaxel for locally recurrent or metastatic squamous cell carcinoma of the anal canal (POD1UM-303/InterAACT-2): a global, phase 3 randomised controlled trial. Rao, Sheela et al.The Lancet, Volume 405, Issue 10495, 2144 - 2152

THIS PROTOCOL HAS BEEN DIRECTED BY DR DEBBIE WILLIAMSON, DESIGNATED LEAD CLINICIAN FOR COLORECTAL CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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