

Durvalumab Gemcitabine Carboplatin

(Neo/adjuvant bladder)

Indication

Neoadjuvant and adjuvant bladder cancer

Carboplatin regimen only for patients that cannot tolerate Cisplatin. Cisplatin associated with better response in clinical trials.

Regimen details

Cycles 1-4

Durvalumab 1500mg intravenous infusion

Day	Drug	Fluid	Time
1	Durvalumab	100ml 0.9% sodium chloride	1 hour
1	Carboplatin (AUC 5)	500mls 5% Glucose	30-60 mins
1 & 8	Gemcitabine 1000mg/m ²	250ml 0.9% Sodium chloride	30 Mins

Cycle 5-12

Durvalumab 1500mg intravenous infusion only

Cycle frequency

Cycles 1-4 are given every 21 days

Cycles 5-12 are given every 28 days

Number of cycles

As above

Administration

Durvalumab is given in 100ml 0.9% sodium chloride over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter Patients should be monitored for signs and symptoms of infusion-related reactions.

Gemcitabine is given intravenously over 30 minutes. Giving more slowly may increase the toxicity

Carboplatin is given in 500ml 5% dextrose 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 carboplatin.

Facilities for the treatment of hypotension and bronchospasm must be available.

If hypersensitivity reactions occur, refer to the alliance protocol for management of hypersensitivity

Pre-medication

As per antiemetic guidelines

Emetogenicity

Carboplatin: moderate

Gemcitabine: low

Durvalumab: minimal

Additional supportive medication

None

Extravasation

Carboplatin - irritant
Gemcitabine – neutral
Durvalumab - neutral

Investigations – pre first cycle

Standard network pre-SACT tests

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST)

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	$\geq 1.0 \times 10^9/L$
Platelet count	$\geq 100 \times 10^9/L$
Creatinine clearance	$\geq 30 \text{ mL/min}$
Bilirubin	$\leq 1.5 \times \text{ULN}$
ALT/AST	$< 3 \times \text{ULN}$

Immunotherapy toxicity

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/acute-oncology-crg-metastatic-spinal-cord-compression-mscc-crg>

Dose modifications

Do not adjust dose of durvalumab

Haematological toxicity

Day 1:

If neutrophils $< 1.0 \times 10^9 /L$ and/or platelets $< 100 \times 10^9 /L$ delay by 1 week and recheck FBC

Reduce carboplatin and gemcitabine to 75% doses if:

- treatment is delayed for > 2 weeks due to haematological toxicity
- grade 4 neutropenia with fever
- grade 4 thrombocytopenia > 3 days
- thrombocytopenia with bleeding
- afebrile grade 4 neutropenia (add prophylactic ciprofloxacin 500mg BD for 7 days for subsequent cycles)

Day 8:

Neutrophils		Platelets	Gemcitabine Dose
≥ 1.0	AND	≥ 100	100%
0.5–1.0	OR	50–99	75%
< 0.5	OR	< 50	Omit

Renal Impairment

CrCl (mL/min)	Gemcitabine Dose
≥ 60	100%
40–59	100%
< 40	100% (consider dose reduction if $< 30 \text{ mL/min}$)

Hepatic impairment

Lancashire & South Cumbria Cancer Network
Systemic Anticancer Treatment Protocol

Use gemcitabine in caution in hepatic impairment. Raised transaminases do not seem to cause dose limiting toxicity. If bilirubin > 1.5 x ULN, initiate gemcitabine at dose of 800mg/m²

Toxicity	Grade	Carboplatin dose	Gemcitabine dose (days 1 & 8)
Neurotoxicity	<1	100%	100%
	2	50%	100%
	3	Omit	100%
	4	Discontinue	Discontinue
Stomatitis/Mucositis	1	100%	100%
	2	Omit until <grade 1 then 75% dose	Omit until <grade 1 then 75% dose
	3	Omit until <grade 1 then 50% dose	Omit until <grade 1 then 50% dose
	4	Discontinue or omit until ≤ grade 1 then 50% dose	Discontinue or omit until ≤ grade 1 then 50% dose

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

- **Serious side effects**

Immunotherapy toxicity

Myelosuppression

Infertility

Interstitial pneumonitis, ARDS

Cardiotoxicity

Hepatotoxicity

Haemolytic uraemic syndrome*

Ocular toxicity

Ototoxicity

Nephrotoxicity

Peripheral neuropathy

*Gemcitabine should be discontinued at the first sign of microangiopathic haemolytic anaemia (such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevated bilirubin, creatinine, blood urea nitrogen or LDH. Renal failure may not be reversible with discontinuation of therapy, dialysis may be required.

- **Frequently occurring side effects**

Myelosuppression

Nausea and vomiting

Mucositis, stomatitis

Diarrhoea, constipation

Oedema

Haematuria

- **Other side effects**

Raised transaminases

Alopecia

Fatigue

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.

Additional comments

References

Gemcitabine SPC: <https://www.medicines.org.uk/emc/product/7298/smpc>

Carboplatin SPC: <https://www.medicines.org.uk/emc/product/3787/smpc>

THIS PROTOCOL HAS BEEN DIRECTED BY DR PARIKH, CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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Whilst every effort is made to ensure the accuracy of the information in a given protocol it cannot be guaranteed that the protocol is fully up to date. Cancer treatment can be dynamic in nature. Decisions on SACT must therefore be based on the independent judgement of the clinician with reference to changing information on the medicine (eg, available literature and SmPC) and evolving medical practices.
