Durvalumab Gemcitabine Cisplatin (Neo/adjuvant bladder)

Indication

Neoadjuvant and adjuvant bladder cancer

Regimen details

Cycles 1-4

Day	Drug	Route	Fluid	Time
1	Durvalumab 1500mg	IV	100ml 0.9% sodium chloride	1 hour
		IV	1litre 0.9% sodium chloride +20mmol potassium chloride +10mmol magnesium sulphate	2 hours
	Cisplatin 70mg/m^2	IV	1 litre 0.9% sodium chloride	2 hours
		IV	1litre 0.9% sodium chloride +20mmol potassium chloride +10mmol magnesium sulphate	2 hours
	Gemcitabine 1000mg/m^2	IV	250ml 0.9% NaCl	30 mins
8	Gemcitabine 1000mg/m^2	IV	250ml 0.9% NaCl	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
Cisplatin is given over 2 hours with hydration before and after as shown above

Pre-medication

As per antiemetic guidelines

Emetogenicity

Cisplatin: high
Gemcitabine: low
Durvalumab: minimal

Additional supportive medication

None

Extravasation

Cisplatin – exfoliant
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	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 60 mL/min
Bilirubin	≤ 1.5 x ULN
ALT/AST	< 3 x 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 x 10^9 /L and/or platelets < 100 x 10^9 /L delay by 1 week and recheck FBC

Reduce cisplatin 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)	Cisplatin Dose	Gemcitabine Dose
≥60	100%	100%
40–59	Split dose on days 1 & 8	100%
<40	Omit	100% (consider dose reduction if <30ml/min)

Hepatic impairment

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/m^2

Toxicity	Grade	Cisplatin dose	Gemcitabine dose (days 1 & 8)
Neurotoxicity	<1	100%	100%
	2	50%	100%
	3	Omit	100%
	4	Discontinue	Discontinue
Stomatitis/Mucostitis	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.

Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity when given within 2 weeks of cisplatin.
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Ototoxic drugs: increased risk of ototoxicity

Phenytoin: cisplatin reduces absorption and efficacy of phenytoin, monitor levels and adjust dose as necessary.
Anti-gout agents: cisplatin may increase plasma concentration of uric acid therefore dose adjustments may be required to control hyperuricaemia and gout.

Additional comments

References

Gemcitabine SPC: https://www.medicines.org.uk/emc/product/7298/smpc
Cisplatin SPC: https://www.medicines.org.uk/emc/product/100546/smpc
Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer. Powels et al. N Engl J Med 2024;391:1773-1786

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.
