Durvalumab, Cisplatin & Gemcitabine (Biliary Tract)

Indication

Locally advanced, unresectable or metastatic biliary tract cancer

(NICE TA944)

ICD-10 codes

Codes prefixed with C23

Regimen details

Combination phase

Day	Drug	Dose	Route
1	Durvalumab	1500mg	IV infusion
1 & 8	Cisplatin	25mg/m^2	IV infusion
1 & 8	Gemcitabine	1000mg/m^2	IV infusion

Maintenance phase

Day	Drug	Dose	Route
1	Durvalumab	1500mg	IV infusion

Cycle frequency

Combination durvalumab and chemotherapy: 21 days
Maintenance durvalumab: 28 days

Number of cycles

Combination durvalumab and chemotherapy: up to 8 cycles
Maintenance durvalumab: until disease progression or unacceptable toxicity

Administration

Durvalumab is administered over 60 minutes, diluted in sodium chloride 0.9% or glucose 5%, to a final concentration of 1-15 mg/mL.

Durvalumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding 0.2 or 0.22 micron filter.

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusion for infusion related reactions. For grade 1-2 infusion related reactions, decrease the infusion rate and closely monitor or temporarily interrupt treatment. Premedication with paracetamol and chlorphenamine should be used for further doses and patient should be closely monitored. For grade 3-4 infusion related reactions permanently discontinue treatment.

Gemcitabine is administered in 250-500mL sodium chloride 0.9% over 30 minutes.

Cisplatin is administered in 500mL sodium chloride 0.9% over 60 minutes following the pre and post hydration protocol below.

Infusion Fluid & Additives	Volume	Infusion Time
Sodium Chloride 0.9% + 2g $MgSO_4$ + 20mmol KCl	1000mL	1 hour
Ensure urine output > 100mL / hour prior to giving cisplatin. Give a single dose of furosemide 20mg iv if necessary.		
Cisplatin	500mL	1 hour
Sodium Chloride 0.9%	500mL	30 minutes
TOTAL	**2000mL**	**2 hours 30 minutes**

Note: Patients with magnesium or potassium below normal range should have 2g $MgSO_4$ and 20mmol KCl added to the post-hydration bag, the volume increased to 1000mL and the duration of the infusion increased to 2 hours.

All patients must be advised to drink at least 2 litres of fluid over the following 24 hours.

Pre-medication
Nil

Emetogenicity
This regimen has moderate-high emetic potential – refer to local policy

Additional supportive medication
Mouthwashes as per local policy.
Loperamide if required.

Extravasation
Durvalumab is neutral (Group 1)
Cisplatin is an exfoliant (Group 4)
Gemcitabine is neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
Calcium	14 days
Glucose	14 days
Thyroid function	14 days
Cortisol	14 days

Investigations – pre combination treatment cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours*
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days
Calcium	7 days
Glucose	As clinically indicated
Thyroid function	6 weekly
Cortisol	At consultant discretion

* Additional FBC required within 24 hours of day 8

Investigations – pre maintenance durvalumab cycles

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days
Calcium	7 days
Glucose	As clinically indicated
Thyroid function	6 weekly
Cortisol	At consultant discretion

Standard limits for administration to go ahead

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

Investigation	**Limit**
Neutrophils	> 1.0 x 10^9/L
Platelets	> 100 x 10^9/L
Bilirubin	< 1.5 x ULN
Creatinine Clearance (CrCl)	≥ 45mL/min
ALT/AST	< 3 x ULN

Dose modifications

Dose reductions are not recommended for durvalumab. Doses should be delayed or discontinued based on tolerability.

- **Haematological toxicity**

Neutrophils (x10^9/L)		**Platelets** (x 10^9/L)	**Cisplatin dose**	**Gemcitabine dose**
>1.0	and	>100	100%	100%
0.5-1.0	or	50-100	100%	75%
<0.5	or	<50	omit	omit

In the case of febrile neutropenia restart cisplatin at 100% and gemcitabine at 75% dose.

Durvalumab: discuss with consultant if neutrophils < 1 x 10^9/L or platelets < 75 x 10^9/L

- **Renal impairment**

Durvalumab: No dose modifications required in mild-moderate renal impairment (CrCl ≥ 30ml/min). There is limited data of use in patients with severe renal impairment - use with caution. See below for management of treatment related nephritis.

Cisplatin:

CrCl (mL/min)	**Cisplatin dose**	**Gemcitabine dose**
≥ 45	100%	100%
30-44	Omit*	100%
< 30	Omit*	Consider dose reduction (consultant decision)

*consider switching to carboplatin AUC 2 if CrCl < 45ml/min.

Gemcitabine: consider dose reduction if CrCl < 30ml/min – discuss with consultant

- **Hepatic impairment**

Durvalumab: No modifications required for mild or moderate hepatic impairment. There is limited data on use of durvalumab in severe hepatic impairment but no need for dose adjustment is expected. See below for management of hepatitis emergent on treatment.

Cisplatin: no dose reduction required

Gemcitabine: Lack of information available on the use of gemcitabine in patients with hepatic impairment, therefore, used with caution. If bilirubin > 1.5 x ULN, consider reducing dose to 80% (consultant decision).

- **Other toxicities**

Cisplatin

Neurotoxicity or ototoxicity:

- ≥ Grade 2: permanently stop cisplatin and switch to carboplatin AUC 2.

Gemcitabine

Stomatitis:

- Grade 3: reduce gemcitabine to 75% dose.

Durvalumab

Immune reactions may occur during or after completion of treatment. Patients must be advised to seek specialist advice if they experience significant side effects as these can worsen rapidly.

Please refer to local guidelines for the management of immunotherapy toxicities.

For suspected immune related adverse events, durvalumab should be withheld and corticosteroids administered. Once symptoms have resolved to ≤ Grade 1 the corticosteroid dose should be tapered over 1 month.

If no improvement within 3 to 5 days despite corticosteroids, start additional immunosuppressive therapy as per local policy. Once resolved to Grade 0, corticosteroid taper should be initiated and continued over at least 1 month, after which durvalumab may be resumed based on clinical judgment.

Permanently discontinue treatment if adverse reaction does not resolve to ≤ Grade 1 within 30 days.

For non-immune-mediated Grade 2-3 adverse reactions, consider withholding treatment until ≤ Grade 1 or baseline. For any Grade 4 adverse reactions discontinue treatment.

Toxicity	Definition	Dose adjustment
Pneumonitis/ interstitial lung disease	Grade 2	Withhold
	Grade 3-4	Permanently discontinue
Hepatitis	Bilirubin 1.5-3 x ULN and/or AST/ALT 3-10 x ULN	Withhold
	Bilirubin > 3 x ULN or AST/ALT > 10 x ULN	Permanently discontinue
	Concurrent bilirubin > 2 x ULN and AST/ALT 3 x ULN and with no other cause	Permanently discontinue
Colitis or diarrhoea	Grade 2-3	Withhold
	Grade 4	Permanently discontinue
Hypothyroidism	Grade 2-4	Organise thyroid hormone replacement therapy and continue treatment
Hyperthyroidism	Grade 2-4	Withhold until clinically stable
Adrenal insufficiency Hypophysitis or Hypopituitarism	Grade 2-4	Withhold until clinically stable
Immune mediated Type 1 diabetes mellitus	Grade 2-4	Withhold until clinically stable
Nephritis	Grade 2 (creatinine 1.5 - 3 x ULN or baseline)	Withhold
	Grade 3 (creatinine 3-6 x ULN or 3 x baseline) Grade 4 (creatinine 6 x ULN)	Permanently discontinue
Rash	Grade 2 (> 7 days) or Grade 3	Withhold
	Grade 4	Permanently discontinue
Myocarditis	Grade 2	Withhold
	Any Grade with positive biopsy Grade 3-4	Permanently discontinue
Myositis/ polymyositis	Grade 2-3	Withhold
	Grade 4	Permanently discontinue
Myasthenia gravis, Guillain-Barre syndrome, Encephalitis	Grade 2-4	Permanently discontinue
Transverse myelitis	Any grade	Permanently discontinue
Meningitis	Grade 2	Withhold
	Grade 3-4	Permanently discontinue
Infection	Grade 3-4	Withhold until clinically stable
Other immune reactions	Grade 2-3	Withhold
	Grade 4	Permanently discontinue

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

- **Serious side effects**

Colitis
Hepatitis
Peripheral neuropathy
Endocrinopathies
Nephritis
Interstitial lung disease/pneumonitis
Pancreatitis
Myocarditis
Myelosuppression
Infertility

- **Frequently occurring side effects**

Myelosuppression
Infusion-related reactions
Pyrexia
Pruritus
Rash
Nausea and vomiting
Diarrhoea, constipation
Abdominal pain
Raised liver function tests
Fatigue
Decreased appetite
Hypo / Hyperthyroidism
Abdominal pain
Uveitis / Dry eyes
Stomatitis, mucositis
Myalgia / Myositis
Peripheral neuropathy
Ototoxicity
Oedema

- **Other side effects**

Adrenal insufficiency
Type 1 diabetes mellitus
Hypopituitarism
Hyperglycaemia
Tumour pain
Raised transaminases
Nail changes
Taste disturbance
Skin reactions

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

Corticosteroids: use of systemic corticosteroids at baseline, before starting durvalumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of the agent. However, systemic corticosteroids or other immunosuppressants can be used after starting durvalumab to treat immune-related adverse reactions.

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

Cisplatin: Avoid ototoxic and nephrotoxic agents (including aminoglycosides, loop diuretics and amphotericin B) as these may increase toxicity of cisplatin.
Allopurinol and antigout agents: Cisplatin may increase the concentration of blood uric acid. Thus, in patients concurrently receiving **antigout agents** such as allopurinol, colchicine, probenecid or sulfinpyrazone, dosage adjustment of these drugs may be necessary to control hyperuricemia and gout.

Additional comments

The patient will be issued with a durvalumab patient alert card and advised to carry the card at all times.

Contraception: Adequate methods of contraception should be used during therapy and for at least 3 months after the last dose of durvalumab.

References

- National Institute for Health and Care Excellence TA944 accessed 25 January 2024 via www.nice.org.uk
- Summary of Product Characteristics Durvalumab (AstraZeneca) accessed 25 January 2024 via www.medicines.org.uk
- Summary of Product Characteristics Cisplatin (Hospira) accessed 25 January 2024 via www.medicines.org.uk
- Summary of Product Characteristics Gemcitabine (Lilly) accessed 25 January 2024 via www.medicines.org.uk
- Oh, D-Y. et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evid 2022; 1(8)

Written/reviewed by: Dr S Falk (Consultant Oncologist, UHBW NHS Trust)

Checked by: Kate Gregory (Lead Pharmacist for SACT protocols, SWAG Cancer Alliance)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)

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