(R) GDP - Gemcitabine, Dexamethasone and Cisplatin +/- Rituximab

Indication

Treatment of relapsed / refractory Hodgkin Lymphoma and aggressive Non-Hodgkin Lymphoma.
First line therapy for peripheral T cell lymphoma.

In combination with rituximab in B cell malignancies.

ICD-10 codes

Codes with a prefix C81-86

Regimen details

Day	Drug	Dose	Route
1	Rituximab*	375mg/m^2	IV infusion
1 and 8	Gemcitabine	1000mg/m^2	IV infusion
1 to 4	Dexamethasone	40mg	IV or PO
1	Cisplatin	75mg/m^2	IV

* if appropriate

When used for priming prior to stem cell collection: Daily G-CSF days 9-15 (dose as per local policy). Continue G-CSF until harvesting completed. Aim to collect days 15 +/- 16.

Cycle frequency

21 days

Number of cycles

Up to 3 cycles

Administration

Day 1

Rituximab is administered in 500mL sodium chloride 0.9%. The first infusion should be initiated at 50mg/hour and if tolerated the rate can be increased at 50mg/hour every 30 minutes to a maximum of 400mg/hour. Subsequent infusions should be initiated at 100 mg/hour and if tolerated increased at 100mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Gemcitabine is administered in 250-500mL sodium chloride 0.9% over 30 minutes. Note: gemcitabine may be given during pre-hydration for cisplatin (see below).

Cisplatin is administered in 500mL sodium chloride 0.9% over 1 hour following the pre and post hydration protocol below (or according to local hydration policy).

If patient has bulky disease consider pre hydration with sodium chloride 0.9% 1 litre over 4-6 hours.

Infusion Fluid & Additives	Volume	Infusion Time
Sodium Chloride 0.9%	1000mL	1 hour
Mannitol 20% **OR** Mannitol 10%	200mL 400mL	30 minutes 30 minutes
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% + 2g $MgSO_4$ + 20mmol KCl	1000mL	2 hours
TOTAL	**2700mL or 2900mL**	**4 hours 30 minutes**

Patients with low magnesium levels (<0.7 mmol/L) should have an additional 2g (8mmol) magnesium sulphate added to the pre-hydration bag.

An accurate fluid balance record must be kept.

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

Day 8
Gemcitabine administered in 250-500mL sodium chloride 0.9% over 30 minutes.

Pre-medication

Antiemetics as per local policy.
Rituximab premedication:

- Paracetamol 500mg- 1g PO 60 minutes prior to rituximab infusion
- Chlorphenamine 10mg IV bolus 15-30 minutes prior to rituximab infusion
- Dexamethasone 8mg IV bolus or Hydrocortisone 100mg IV bolus 15-30 minutes prior to rituximab infusion (may be omitted if day 1 dexamethasone has been taken at least 30 minutes prior to the start of the rituximab infusion)

Emetogenicity

Day 1 has high emetic potential
Day 8 has low emetic potential

Additional supportive medication

Allopurinol 300mg OD (100mg OD if CrCl < 20mL/min) for the first 2 weeks of cycle 1.
Antiviral, antifungal and PCP prophylaxis as per local policy.
Prophylactic antibiotics may be required e.g. ciprofloxacin (or as per local policy) from day 8 to day 14 of each cycle.
H_2 antagonist or proton-pump inhibitor if required.
If magnesium levels < normal reference range refer to local magnesium replacement guidelines.

Extravasation

Rituximab and gemcitabine are neutral (Group 1)
Cisplatin is an exfoliant (Group 4)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC + clotting screen	14 days
U+E (including creatinine)	14 days
LFTs	14 days
LDH	14 days
Albumin	14 days
Magnesium	14 days
Calcium	14 days
Glucose	14 days
Pregnancy test (women of child bearing potential)	7 days

Other investigations:
Hepatitis B (surface antigen and core antibody status)and C serology
HIV 1 and 2 antibody screen
EBV, CMV and VZV serology
ECG +/- echocardiogram if clinically indicated.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	72 hours*
U+E (including creatinine)	72 hours
LFTs	72 hours
Magnesium	72 hours
Calcium	72 hours
Pregnancy test (women of child bearing potential)	72 hours

*In addition FBC is required on day 8 (or within 24 hours) prior to gemcitabine

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	≥ 75 x 10^9/L
Haemoglobin	≥ 100 x g/L
Creatinine clearance (CrCl)	≥ 60mL/min
Bilirubin	< 1.5 x ULN
ALT/ AST	< 2.5 x ULN

Dose modifications

- **Haematological toxicity**

Day 1:

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Action**
≥1.0	and	≥ 75	100% doses
≥1.0	and	< 75	Delay 1 week If platelets > 50 x 10^9/L 100% doses with platelet transfusion support if necessary
<1.0	and	≥ 75	Delay 1 week If neutrophils > 0.5 x 10^9/L 100% doses with GCSF support
<1.0	and	< 75	Delay 1 week If platelets > 50 x 10^9/L and neutrophils > 0.5 x 10^9/L 100% doses with platelet transfusions and GCSF support If platelets < 50 x 10^9/L and/or neutrophils < 0.5 x 10^9/L repeat blood tests every 3 days and defer until recovery.

Day 8:

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Gemcitabine dose**
≥1.0	and	≥ 75	100%
0.5-<1.0	and	≥ 75	100% with GCSF support Or 75%
		50-<75	75%
<0.5	or	< 50	Omit and commence GCSF

- **Renal impairment**

CrCl (mL/min)	**Cisplatin dose**	**Gemcitabine dose**
≥ 60	100%	100%
50 - 59	75%	100%
40 – 49	50%	100%
< 40	Omit	100%*

*If CrCl <30mL/min consider gemcitabine dose reduction.

Consider substituting cisplatin with carboplatin if CrCl <45 mL/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 800 mg/m^2.

- **Other toxicities**

Toxicity	Definition	Cisplatin dose	Gemcitabine dose
Neurotoxicity	≤Grade 1	100%	100%
	Grade 2	50%	100%
	Grade 3	Omit	100%
	Grade 4	Discontinue	Discontinue
Stomatitis/Mucositis	Grade 1	100%	100%
	Grade 2	Omit until ≤ grade 1 then 75% dose	Omit until ≤ grade 1 then 75% dose
	Grade 3	Omit until ≤ grade 1 then 50% dose	Omit until ≤ grade 1 then 50% dose
	Grade 4	Discontinue or omit until ≤ grade 1 then 50% dose	Discontinue or omit until ≤ grade 1 then 50% dose
Other toxicities (except alopecia or nausea and vomiting)	≤Grade 2	100% (with or without treatment delay)	100% (with or without treatment delay)
	≤Grade 3	Delay until recovery then consider dose reduction (consultant decision)	Delay until recovery then consider dose reduction (consultant decision)

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

- **Serious side effects**

Myelosuppression
Infertility
Interstitial pneumonitis, ARDS
Cardiotoxicity
Hepatotoxicity
Haemolytic uraemic syndrome (HUS)
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.

Cisplatin only:
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.
Lithium: cisplatin may affect lithium plasma levels – monitor.

Additional comments

References

- Summary of Product Characteristics Cisplatin (Hospira) accessed 12 February 2019 via www.medicines.org.uk
- Summary of Product Characteristics Gemcitabine (Lilly) accessed 12 February 2019 via www.medicines.org.uk
- Baetz T., et al (2003) Gemcitabine, dexamethasone and cisplatin is an active and non-toxic chemotherapy regimen in relapsed or refractory Hodgkin's disease. Annals of Oncology 14: 1762–1767.

Written/reviewed by: Dr Lisa Lowry (Consultant Haematologist, UH Bristol NHS Trust), Dr Nikesh Chavda (Bone marrow transplant/IEC fellow, UH Bristol NHS Trust) and Andrea Preston (Haematology Pharmacist, UH Bristol NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Clinical Network)

Date: January 2015 v2 January 2020