Thames Valley
Strategic Clinical Network

Gem-Ox [+/-R]

INDICATION

LYMPHOMA [ICD-10 codes: C81, C83]

- Gem-Ox: Relapsed/Refractory Hodgkin Lymphoma for patients not fit for high dose therapy (e.g., GDP) [Off-label-use* / NHSE funded]
- R-Gem-Ox: Relapsed/Refractory Diffuse Large B-Cell Lymphoma for patients not fit for high dose therapy (e.g., R-GDP) [Licensed indication (R) / Off-label use* (Gem-Ox) / NHSE funded]

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage and IPI of disease - CT scan (neck, chest, abdomen and pelvis), and/or PET-CT, presence or absence of B symptoms, clinical extent of disease, consider bone marrow aspirate and trephine.
3. Blood tests – FBC, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, β_2 microglobulin, hepatitis B core antibody and hepatitis B surface Ag, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save.
4. **Hodgkin lymphoma patients** – ensure the requirement for **irradiated blood products** from time of diagnosis for all future transfusions has been flagged to the transfusion laboratory and that irradiation card is attached to the patient's notes and copy has been given to the patient. See 'Guidelines for the use of Blood Components in Adult Haematology' [Link]
5. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
6. ECG +/- Echo *if clinically indicated*.
7. Record performance status (WHO/ECOG).
8. Record height and weight.
9. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
10. Fertility - it is very important the patient understands the potential risk of infertility. All patients should be offered fertility advice by referring to the Oxford Fertility Unit.
11. Hydration – *in patients with bulky disease* pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. Refer to the Tumour Lysis Syndrome in Adults protocol (H.8).
12. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
13. Treatment should be agreed in the relevant MDT.
14. Consider inserting a central venous catheter or PICC line if poor venous access.

DRUG REGIMEN

Day(s)	Drug	Dose	Route	Administration details
1	**Pre-medications (at least 30 minutes before rituximab)**			
	Hydrocortisone sodium succinate Chlorphenamine Paracetamol	100mg 10mg 1000mg	IV bolus IV bolus PO	
1	**RITUXIMAB**	375mg/m^2	IV infusion	In 500mL sodium chloride 0.9% *[Refer to Protocol Care Plans Rituximab infusion rates, max. rate 400mg/hour]*
1	**GEMCITABINE**	1000mg/m^2	IV infusion	in 250mL sodium chloride 0.9% over 30 minutes
1	**OXALIPLATIN**	100mg/m^2	IV infusion	in 250-500mL glucose 5% over 2 hours [concentration 0.2-0.7mg/ml]
CYCLE FREQUENCY: 14 days*				
DURATION: maximum 6 cycles				

*Note: Low threshold is recommended to extend to 3-weekly cycles based on toxicities.

RESTAGING

Give 3-4 courses and restage with CT.
If partial or complete remission, continue to 6 courses of (R)-GemOx.

DOSE MODIFICATIONS

Haematological Toxicity

Each cycle should normally only be given if platelets > 100 x 10^9/L and neutrophils > 1 x 10^9/L.
If neutrophils <1 x 10^9/L or platelets <100 x 10^9/L, delay treatment by one week or until counts recovery.
Gemcitabine may be reduced to 750mg/m^2 at consultant's discretion to maintain dose intensity.
Consider addition of G-CSF to subsequent cycles.

Neuropathic Toxicity

Peripheral sensory neuropathy usually occurs after a cumulative oxaliplatin dose of 800mg/m^2 but can also occur at an earlier stage. It can occur during or after treatment with oxaliplatin. It is usually reversible but may take 3 – 5 months to recovery.

Grade 2 sensory or motor neuropathy resolved before beginning of the next cycle	Reduce oxaliplatin dose to 75mg/m^2
Grade 3 or above sensory or motor neuropathy or **Grade 2** but not resolved before beginning of the next cycle	Omit oxaliplatin until symptoms improve then restart at 75mg/m^2
Acute laryngo-pharyngeal dysaesthesia	Extend oxaliplatin infusion to over 6 hours

Renal / Hepatic Impairment

	Renal impairment	Hepatic impairment
Gemcitabine	GFR ≥ 30ml/min: 100% dose CrCl < 30mL/min: No data, consider dose reduction – clinical decision	Bilirubin < 27 µmol/L: 100% dose Bilirubin ≥ 27 µmol/L: start at 80% dose and increase the dose if tolerated
Oxaliplatin	GFR ≥ 30 ml/min: 100% dose GFR < 30 ml/min: contraindicated (SmPC), off-label: consider 50% dose	No data – clinical decision

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients. Refer to the Summary of Product Characteristics (SmPCs).
- Oxaliplatin: peripheral sensory neuropathy with functional impairment prior to first course. Severely impaired renal function (CrCl < 30 mL/min). Previous exposure to oxaliplatin within last 12 months.

SPECIAL WARNINGS / PRECAUTIONS

Oxaliplatin

- **Extravasation:** Oxaliplatin is an exfoliant. Follow oxaliplatin-specific pathway in the TVCA Extravasation Guideline for treatment.
- **Acute neurosensory manifestations** start within hours of administration and often occur on exposure to cold. They commonly present as transient paresthesia of hands & feet, dysaesthesia and hypoesthesia (up to 95% patients). Symptoms usually resolve within minutes to days. No treatment is usually required. Advise patient to avoid exposure to cold air or drinks.
- **Acute laryngopharyngeal dysaesthesia** occurs in 1% --2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing). The symptoms are rapidly reversible even in the absence of treatment. Subsequent infusion should be given over 6 hours to reduce the incidence. Gemcitabine and oxaliplatin can be scheduled on Day 2 of each cycle if time is limited for Treatment Day Unit.
- **Hypersensitivity reactions** may occur during oxaliplatin infusion. It can be distinguished from acute laryngopharyngeal dysaesthesia with the presence of bronchospasm, laryngospasm, decreased O_2 saturation and pruritus. Stop oxaliplatin infusion and seek medical help immediately. Treat with chlorphenamine 10mg IV and hydrocortisone 100mg. Oxygen, adrenaline, bronchodilators and fluid should be given as appropriate. Cross-sensitivity with other platinum products has been reported.

INVESTIGATIONS

FBC, U&Es and LFTs

CONCURRENT MEDICATION

Allopurinol	300mg daily for 7 days [Cycle 1 only] unless otherwise indicated in TLS risk assessment. Refer to the Tumour Lysis Syndrome in Adults protocol (H.8)
H2 antagonist or PPI - discuss with consultant	Famotidine 20mg twice daily or Omeprazole 20mg once daily for the duration of treatment
Aciclovir	200mg three times a day for duration of treatment and for 3 months after completion
PCP prophylaxis	Co-trimoxazole 960mg three times a week, on Mon / Wed / Fri for duration of treatment and for 3 months afterwards (consider reducing the dose during neutropenic periods). PCP prophylaxis should be considered especially for high risk patients (e.g., prior PJP, concurrent prolonged steroids [20mg prednisolone equivalent per day for >3 weeks], heavily pre-treated with persistent lymphopenia).
Filgrastim*	0.5 million units/kg SC OD from day 5 for 7 days if required (*or equivalent G-CSF as per local formulary)

EMETIC RISK

High

INTERACTIONS

(Consult with pharmacist and refer to SmPC for full details)

Anti-hypertensives	Hypotension may occur during rituximab administration, therefore consideration should be given to withholding anti-hypertensives 12 hours prior to the rituximab infusion.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

(Consult with pharmacist and refer to SmPC for full details)

Very commonly reported with regimen: neutropenia, thrombocytopenia, anaemia, infection and nausea.

Rituximab - infusion related reactions or severe cytokine release syndrome characterised by severe dyspnoea, often accompanied by bronchospasm, hypoxia, fever, chills, rigors, urticaria, and angioedema
- hepatitis B reactivation – see pathway for treatment and management of HBV positive patient [Link]

Gemcitabine - alopecia, peripheral odema, cardiac and/or vascular disorders, pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or adult respiratory distress syndrome (ARDS)), renal failure (uncommon, but may not be reversible)

Oxaliplatin - deranged liver enzymes, alopecia, peripheral neuropathy, laryngopharyngeal dysesthesia, hypersensitivity, extravasation.

EXTRAVASATION RISK

Gemcitabine: neutral
Oxaliplatin: exfoliant
Rituximab: neutral

TREATMENTRELATED MORTALITY

< 5%

REFERENCES

1. Mounler et al (2013) Rituximab plus gemcitabine and oxaliplatin in patients with refractory/ relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. Haematologica 98(11):1726-1731
2. Gutierrez A, Rodriguez J, Martinez-Serra J, Gines J, Paredes P, Garcia F, Vercher J, Balanzat J, Del Campo R, Galan P, Morey M, Sampol A, Novo A, Bento L, García L, Bargay J, Besalduch J. Gemcitabine and oxaliplatinum: an effective regimen in patients with refractory and relapsing Hodgkin lymphoma. Onco Targets Ther. 2014 Nov 13;7:2093-100.
3. Sandoz Limited. Rixathon® (rituximab) 500mg concentrate for solution for infusion. Summary of Product Characteristics (SmPC). Last updated 24/06/2022. Available at https://www.medicines.org.uk/emc/ <Last accessed 07/07/2022>
4. Accord Healthcare Limited. Gemcitabine100 mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics (SmPC). Last updated 18/03/2019. Available at https://www.medicines.org.uk/emc/ <Last accessed 07/07/2022>
5. Hospira UK Ltd. Summary of Product Characteristics (SmPC). Oxaliplatin Hospira 5 mg/ml concentrate for solution for infusion. Last updated 13/04/2021. Available at https://www.medicines.org.uk/emc/ <Last accessed 07/07/2022>
6. Krens S D et al (2019). Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol; 20: e201–08

REVIEW

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung (Haematology Pharmacist) Graham Collins (Consultant Haematologist)	New document	Jun 2018	1.0	
Cheuk-kie Jackie Cheung (Haematology Pharmacist)	Ranitidine duration modified	Nov 2018	1.1	
NSSG Lymphoma Group	Annual protocol review	May 2019	1.2	May 2021
NSSG Lymphoma Group Natalia Czub, Haematology Pharmacist, Murali Kesavan, Haematology Consultant	Annual protocol review. Indications, drug regimen, dose modifications, interactions, and references sections updated.	July 2022	2.0	July 2024