

Oxaliplatin and Gemcitabine

Indication

Palliative treatment for relapsed metastatic seminoma, non seminoma or combined tumours.

ICD-10 codes

Codes pre-fixed with C38, C48, C56, C62, C63, C75.3.

Regimen details

| Day | Drug | Dose | Route |
|---------|-------------|-----------------------|-------------|
| 1 and 8 | Gemcitabine | 1000mg/m ² | IV infusion |
| 1 | Oxaliplatin | 130 mg/m ² | IV infusion |

Cycle frequency

21 days

Number of cycles

Usual maximum 6 cycles. Consultant decision to give further cycles.

Administration

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

Oxaliplatin is administered in 250mL glucose 5% over 2 hours.

Oxaliplatin is not compatible with sodium chloride 0.9%. Lines must not be piggybacked or flushed with sodium chloride 0.9% immediately after the infusion.

Patients should be observed closely for platinum hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of oxaliplatin. Facilities for the treatment of hypotension and bronchospasm must be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy: the infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Chlorphenamine 10mg IV may be administered.

Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of oxaliplatin and appropriate therapy should be initiated.

Oxaliplatin may cause transient paraesthesia of hands and feet and laryngopharyngeal dysaesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patients should be advised to take appropriate precautions. This does not require treatment or dose reduction but subsequent infusions should be given over 6 hours.

Pre-medication

Usually none required

Patients who have previously experienced Grade 1 or 2 platinum hypersensitivity should receive the following premedication:

- 45 minutes prior to Oxaliplatin: Dexamethasone 20mg IV
- 30 minutes prior to Oxaliplatin: Chlorphenamine 10mg IV and Ranitidine 50 mg IV

Patients who develop peripheral neuropathy may be considered for calcium gluconate 1g and magnesium sulphate 1g given together in 250mL 5% glucose IV over 20 minutes pre- and post-oxaliplatin infusion. Caution is required in giving this treatment to patients with known hypercalcemia or those receiving therapy with digoxin or thiazide diuretics.

Emetogenicity

This regimen has moderate-high emetic potential.

Additional supportive medication

H₂ antagonist or proton pump inhibitor if required.

Mouthwashes as per local policy.

Oral magnesium supplementation between cycles in addition to the intravenous magnesium administered at the time of chemotherapy if required as per local magnesium replacement guidelines.

Anti-emetics as per local policy.

Consider GCSF as primary prophylaxis from day 9

Extravasation

Oxaliplatin is an exfoliant (Group 4)

Gemcitabine is neutral (Group 1)

Investigations – pre first cycle

| Investigation | Validity period |
|----------------------------|---------------------------|
| FBC | 14 days |
| U+E (including creatinine) | 14 days |
| LFTs | 14 days |
| Magnesium | 14 days |
| Calcium | 14 days |
| AFP, HCG, LDH | 14 days (repeat on day 1) |

Where appropriate offer pre-treatment sperm storage.

Investigations – pre subsequent cycles

| Investigation | Validity period |
|----------------------------|---|
| FBC | 96 hours |
| U+E (including creatinine) | 7 days |
| LFTs | 7 days |
| Magnesium | 7 days |
| Calcium | 7 days |
| AFP, HCG, LDH | 7 days (repeat weekly during treatment) |

Standard limits for administration to go ahead

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

Day 1

| Investigation | Limit |
|-----------------|--|
| Neutrophils | $\geq 1.5 \times 10^9/L^*$ |
| Platelets | $\geq 75 \times 10^9/L^*$ ($\geq 100 \times 10^9/L$ on day 8) |
| Calculated CrCl | > 50 ml/min |
| Bilirubin | $\leq 1.5 \times$ ULN |

Dose modifications

- **Haematological toxicity**

Day 1:

If neutrophils $< 1.5 \times 10^9/L$ or platelets $< 75 \times 10^9/L$ delay for 7 days and if recovered resume at full doses. If more than one delay reduce dose of gemcitabine to 75% for all future doses.

If febrile neutropenia (neutrophils $< 0.5 \times 10^9/L$ and fever requiring IV antibiotics) – reduce all subsequent doses of gemcitabine to 75% and oxaliplatin to $100\text{mg}/\text{m}^2$.

Day 8:

| Neutrophils ($\times 10^9/L$) | | Platelets ($\times 10^9/L$) | Gemcitabine dose |
|---------------------------------|-----|-------------------------------|--|
| ≥ 1.5 | and | ≥ 100 | 100% |
| 1.0 - <1.5 | or | 50 - 99 | 75% |
| < 1.0 | or | < 50 | Omit day 8 and Re-start next cycle with 75% gemcitabine |

- **Renal impairment**

| CrCl (mL/min) | Oxaliplatin dose |
|---------------|------------------|
| ≥ 50 | 100% |
| 30 – 49 | 50 |
| < 30 | Omit |

Gemcitabine

If CrCl $< 30\text{mL}/\text{min}$ consider dose reduction (consultant decision)

- **Hepatic impairment**

Lack of information available on the use of gemcitabine in patients with hepatic impairment, therefore, used with caution. If bilirubin $> 1.5 \times \text{ULN}$, consider reducing dose to $800\text{mg}/\text{m}^2$ (consultant decision).

Oxaliplatin:

Little information available. Probably no dose reduction necessary, consultant decision.

- **Other toxicities**

Oxaliplatin:

If neurological symptoms occur, use the following oxaliplatin dose adjustments:

| Toxicity grade | Oxaliplatin dose |
|---|---------------------------|
| 1 | 100% |
| 2 (persisting until next cycle) | $100\text{mg}/\text{m}^2$ |
| 3 (>7 days but resolved before next cycle) | $100\text{mg}/\text{m}^2$ |
| 3 (persisting until next cycle) or 4 | Discontinue |

Adverse effects - for full details consult product literature/ reference texts**• Serious side effects**

Myelosuppression
Nephrotoxicity
Ototoxicity
Neurotoxicity
Laryngopharyngeal dysaesthesia
Infertility
Haemolytic uraemic syndrome*
Interstitial pneumonitis
Secondary malignancy
Long term risk of cardiovascular disease and metabolic syndrome
Osteonecrosis of the hip

*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

Cold sensitivity
Myelosuppression
Constipation, diarrhoea
Stomatitis, mucositis
Alopecia
Nausea and vomiting
Anorexia

• Other side effects

Raised transaminase
Electrolyte disturbances
Fatigue
Headache

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

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

Antibiotics: The renal toxicity of oxaliplatin is potentiated by aminoglycoside antibacterials (e.g. gentamicin) and amphotericin. Aminoglycosides should be avoided. If aminoglycosides are prescribed, close monitoring of renal function and serum antibiotic levels is required.

Avoid all nephrotoxic drugs where possible

Additional comments

Dose related peripheral sensory neuropathy can occur with oxaliplatin. It usually occurs after a cumulative dose of 800mg/m². It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approximately 3 – 5 months to recovery.

References

- Summary of Product Characteristics Oxaliplatin (Sanofi) accessed 27 April 2016 via www.medicines.org.uk
- Summary of Product Characteristics Gemcitabine (Hospira) 27 April 2016 via www.medicines.org.uk
- Kollmansberger, C. et al. Combination chemotherapy with gemcitabine plus oxaliplatin in patients with intensively pretreated or refractory germ cell cancer: A study of the German testicular cancer study group (2004). J Clin Oncol 22: 108-14
- Pectasides, D. et al. Gemcitabine and oxaliplatin (GEMOX) in patients with cisplatin-refractory germ cell tumours: a phase II study (2004). Ann Oncol; 15:493-97

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