Raltitrexed and Oxaliplatin (Colorectal)

Indication

In patients who are intolerant to 5-fluorouracil or capecitabine, or for whom these drugs are not suitable, e.g. in patients developing cardiotoxicity.

- First line neo-adjuvant or adjuvant treatment of stage III colorectal cancer (Note: Raltitrexed is not licensed for this indication and should only be considered if absolute contraindication to capecitabine or fluorouracil)
- Advanced and/or metastatic colorectal cancer

Regimen details

Day	Drug	Dose	Route
1	Raltitrexed	3mg/m^2	IV infusion
1	Oxaliplatin	130mg/ m^2	IV infusion

Cycle frequency

21 days

Number of cycles

Neo-adjuvant/Adjuvant: 4 cycles
Metastatic: continue until disease progression or unacceptable toxicity

Administration

Raltitrexed is administered in 100mL sodium chloride 0.9% over 15minutes.

Oxaliplatin is administered in 500ml of 5% glucose over 2 hours. Oxaliplatin is not compatible with sodium chloride 0.9%. Lines must not be pig-backed 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 localized 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. Chlorpheniramine 10mg IV may be administered.
Severe reactions such as hypotension, bronchospasm or generalized 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 well advised on precautions to be taken. This does not require treatment or dose reduction but subsequent infusions should be given over 6 hours.

Pre-medication

Antiemetics as per local policy
Patient who have previously experienced Grade 1 or Grade 2 platinum hypersensitivity should receive the following pre-medication:

- 30 minutes prior to oxaliplatin: Dexamethasone 20mg IV
- 30 minutes prior to oxaliplatin: Chlorpheniramine 10mg IV and Ranitidine 50mg IV

Emetogenicity

This regimen has a moderate- high emetogenic potential

Additional supportive medication

Mouthwashes as per local policy. Loperamide if required.
Metoclopramide 10mg tds prn.

Extravasation

Raltitrexed is an inflammatant (Group 2)
Oxaliplatin is an exfoliant (Group 4).

Investigations – pre first cycle

Investigation	**Validity period**
FBC	14 days
U+E (including creatinine)	14 days
LFTs (including AST)	14 days
Calcium	14 days
Magnesium	14 days
CEA	14 days
Hepatitis B serology (HBsAG, HBcAb)	none
HbA1c	3 months
Random glucose	14 days
Calculated Creatinine Clearance	14 days

Investigations - pre subsequent cycles

Investigation	**Validity period**
FBC	96 hours
U+E (including creatinine)	7 days
LFTs (including AST)	7 days
Calcium	7 days
Magnesium	7 days
CEA	7 days
Random glucose	7 days
Calculated Creatinine Clearance	7 days

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	≥ 1.5 x 10^9/L (discuss with consultant ≥ 1.0- <1.5)
Platelets	≥ 100 x 10^9/L
Bilirubin	< 5 x ULN
AST/ALT	< 5 x ULN
Creatinine Clearance (CrCl)	≥ 65mL/min (see dose modifications below)

For treatment with neoadjuvant and adjuvant intent consultants may be happy to proceed with Neutrophils ≥1.0 x 10^9/L and should document this.

Dose modifications

- **Haematological toxicity**

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Raltitrexed Dose**	**Oxaliplatin Dose**
≥ 1.5	and	≥ 100	100%	100%
1.0-1.49	and	≥ 100	75%	100%
0.5-1.0	or	< 100	Delay until recovery, then 75%	Delay until recovery then 100mg/m2
<0.5 or febrile neutropenia	or	<10	Delay until recover then 50%	Delay until recovery then 100mg/m2

Defer treatment for 1 weeks if neutrophil count <1.0 x 10^9/L and/or platelets <100 x 10^9/L and delay next cycle until recovery. Recommence with dose modifications as above.

- **Renal impairment**

Creatinine Clearance (mL/min)	**Raltitrexed Dose**	**Oxaliplatin dose**	**Dosing interval**
> 65	100%	100%	21 days
55-65	75%	100%	28 days
30-54	50%	100%	28 days
25-29	50%	50%	28 days
< 25	Omit	50%	28 days

Changing the dosing interval in iQemo will require a change of regimen

- **Hepatic impairment**

Raltitrexed: Transient elevations of liver transaminases may occur with raltitrexed treatment. No dose modification is needed in mild or moderate hepatic impairment, but LFTs should be monitored carefully during treatment.
Raltitrexed is not recommended in severe hepatic impairment (Clinically jaundiced or Bilirubin > 5 x ULN and/or AST/ALT > 5 x ULN).

Oxaliplatin: No dose adjustment is required.

- **Other toxicities**

Raltitrexed:

Toxicity	Definition	Dose adjustment
Diarrhoea*	Grade 1	100%
	Grade 2	Delay until resolved then 75%
	Grade 3	Delay until resolved then 50%
	Grade 4	Discontinue
Mucositis	Grade 1	100%
	Grade 2	Delay until resolved then 75%
	Grade 3	Delay until resolved then 50%
	Grade 4	Discontinue

* Diarrhoea is often associated with myelosuppression, if grade 3-4, check FBC.

Once doses are reduced for toxicity, they must not be re-escalated.

Dose modifications should be made as per the following table:

Toxicity grade	1st occurrence	2nd occurrence	3rd occurrence	4th occurrence
0-1	100%	100%	100%	100%
2	Delay then 100%	Delay then 75%	Delay then 50%	Discontinue
3	Delay then 75%	Delay then 50%	Discontinue	
4	Delay then 50%	Discontinue		

Any delays should be until the toxicity has resolved to grade 0-1.

Oxaliplatin:

Neurological toxicity:

Dose related peripheral neuropathy can occur with oxaliplatin. It usually occurs after a cumulative dose of 800mg/m^2. It can occur once oxaliplatin is completed.

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

Toxicity grade	Oxaliplatin
1 (any duration) or grade 2 longer than 7 days	100%
2 paraesthesia persisting until next cycle	100mg/m^2
3 paraesthesia lasting longer than 7 days	100mg/m^2
3 paraesthesia persisting until next cycle	Discontinue permanently
4 of any duration	Discontinue permanently

In grade 3 or 4 stomatitis or diarrhea, delay until recovers to ≤ grade 2 then reduce oxaliplatin dose to 100mg/m^2.

Patients presenting with diarrhea must be carefully monitored until the symptoms have disappeared as a rapid deterioration can occur.

Any delays should be until toxicity has resolved to grade 0-1

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

- **Serious side effects**

Myelosuppression
Infertility
Allergic reactions
Neurotoxicity

Nephrotoxicity

- **Frequently occurring side effects**

Nausea and vomiting
Diarrhoea
Mucositis
Asthenia
Anorexia
Abdominal pain
Rash
Fatigue
Alopecia

- **Other side effects**

Elevated liver enzymes
Headache
Dizziness
Dysgeusia

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 or NOAC during treatment.

Oxaliplatin:
Avoid nephrotoxic agents as these may increase toxicity of oxaliplatin

Raltitrexed: Folic acid, folinic acid/leucovorin (or vitamin preparations containing these agents) – may reduce efficacy of raltitrexed and should be avoided immediately before and during drug use.

Additional comments

Fertility/Contraception

Raltitrexed is mutagenic. Pregnancy should be avoided if either partner is receiving raltitrexed. It is also recommended that conception should be avoided for at least 6 months after cessation of treatment. Patients should agree to use an acceptable method of birth control to avoid pregnancy for the duration of treatment and for 6 months afterwards.
Breastfeeding should be discontinued during treatment.
Oxaliplatin may have an anti-fertility effect

References

- Summary of Product Characteristics - Raltitrexed accessed 10 JUly 2025 via www.medicines.org.uk
- Gravalos, C. et al. A randomized phase II study to compare oxaliplatin plus 5-fluorouracil and leucovorin (FOLFOX4) versus oxaliplatin plus raltitrexed (TOMOX) as first-line chemotherapy for advanced colorectal cancer. Clin Transl Oncol. 2012:14(8):606-612
- National Institute for Health and Care Excellence. Clinical Guidance 151 accessed 10 July 2025 via www.nice.org.uk
- Summary of Product Characteristics Oxaliplatin accessed 10 July 2025 via www.medicines.org.uk
- Krens S D, Lassche, Jansman GFGA, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20:e201-08. Supplementary appendix

THIS PROTOCOL HAS BEEN DIRECTED BY DR WILLIAMSON DESIGNATED LEAD CLINICIAN FOR COLORECTAL CANCER
RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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