TOMOX - 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 complete DPD deficiency or 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

ICD-10 codes

Codes prefixed with C18-20

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
Advanced/Metastatic: up to 8 cycles

Administration

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

Oxaliplatin is administered in 250-500mL 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 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.

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

Emetogenicity

This regimen has moderate to high emetic potential

Additional supportive medication

Mouthwash and emollients as per local policy.
Antiemetics including dexamethasone.
Loperamide if required.

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	14 days
Calcium	14 days
Magnesium	14 days
CEA	28 days

Investigations – pre subsequent cycles

Investigation	**Validity period**
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Magnesium	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
Platelets	≥ 100 x 10^9/L
Bilirubin	< 5 x ULN (see below)
AST/ALT	< 5 x ULN
Creatinine Clearance (CrCl)	≥ 65mL/min

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

If recurrent neutropenia or thrombocytopenia despite dose reduction, consider further dose reduction to both agents or adding GCSF

- **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

- **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.

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

Grade	Oxaliplatin dose
1	100%
2 (persisting until next cycle)	100mg/m^2
3 (>7 days but resolved before next cycle)	100mg/m^2
3 (persisting until next cycle) or 4	Discontinue

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
Dysgeusia
Dizziness
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 or DOAC during treatment.

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.

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

Additional comments

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.

There is no clinically proven antidote available. In the case of inadvertent or accidental overdose, consider the use of folinic acid at a dose of 25mg/m^2 IV every 6 hours. As the time interval between raltitrexed administration and folinic acid rescue increases, its effectiveness in counteracting toxicity may diminish.

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 recover.

References

- Summary of Product Characteristics - Raltitrexed (Hospira) accessed 20 October 2022 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 20 October 2022 via www.nice.org.uk
- Summary of Product Characteristics Oxaliplatin (Sanofi) accessed 20 October 2022 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

Written/reviewed by: Dr J McKeon (Clinical Oncology Registrar, UHBW NHS Trust), Dr H Brooks (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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