RALTITREXED AND OXALIPLATIN

For use only in patients with a contra-indication to fluoropyrimidines:

a) Metastatic colorectal cancer, as an alternative to Oxaliplatin MdG or Oxali-Cap
b) Adjuvant use in high risk Stage II, and Stage III, colon and rectal cancer

Drug / Dosage:

Patients with CrCl > 65ml/min;

Raltitrexed	3mg/m^2	IV	Day 1
Oxaliplatin	130mg/m^2	IV	Day 1

N.B. For patients with CrCl ≤ 65ml/min, see Renal Impairment section

Administration:

Raltitrexed in 100ml sodium chloride 0.9% over 15 minutes
Flush with glucose 5% then give:
Oxaliplatin in 500ml glucose 5% over 2 hours

Frequency:

3 weekly cycle for patients with CrCl > 65ml/min.
For patients with impaired renal function, reduced dose raltitrexed administered on a 4-weekly cycle, along with 2-weekly oxaliplatin 85mg/m^2 - see Renal Impairment for details.
Advanced use: continue until disease progression or unacceptable toxicity
Adjuvant use: 8 cycles

Main Toxicities:

myelosuppression; mucositis; diarrhoea; rise in liver transaminases; neurotoxicity (see Comments); allergic reactions (see Comments); ovarian failure/infertility

Anti-emetics:

highly emetogenic

Extravasation:

non – vesicants

Regular Investigations:

FBC	Day 1
LFTs	Day 1
U&Es	Day 1
Mg^{2+}	Day 1 (ideally, correct any low Mg^{2+} before oxaliplatin given)
CEA	Day 1
CT scan	after 3 months (metastatic use only)
EDTA	prior to Cycle 1

Comments:

For patients on Cycle 1 whose EDTA is not yet available, Cockcroft & Gault may be used to predict GFR. Doses and scheduling should be adjusted if necessary once EDTA available. EDTA should only be repeated if the result is borderline at the start of treatment or if there is a 30% change in serum creatinine.

Rise in transaminases due to raltitrexed is maximal in Cycles 2 and 3 and then tends to resolve with continued treatment - it should not be interpreted as an indicator of progressive liver disease.

Give routine mouthcare and anti-diarrhoeals for use if required. If severe mucositis occurs, associated with myelosuppression, then patients should be supported with hospitalisation for IV fluid, anti-emetics, anti-diarrhoeals and broad spectrum antibiotics.

Reason for Update: allergic reactions to oxaliplatin and need for Mg and Ca reviewed	Approved by Consultant: Dr S Essapen
Version: 4	Approved by Lead Chemotherapy Nurse: V Mumford
Supersedes: Version 3	Date: 30.12.13
Prepared by: S Taylor	Checked by: C Tucker

Oxaliplatin and Neurotoxicity

Acute - cold-related dysaesthesia (CRD):
Many patients experience transient paraesthesia of hands & feet, and some experience 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 patient should be well advised on precautions to be taken. Does not require treatment or dose reduction.
For laryngopharyngeal dysaesthesia, subsequent infusions should be given over 6 hours. Consideration to infusion of 10mmol of magnesium + 1gram of calcium gluconate in 0.9% sodium chloride 250ml over 1 hour, prior to starting the oxaliplatin, should also be made.
NB. The above management may also benefit patients who complain of pain/weakness in arm during oxaliplatin administration, but should **not** be used to try and alleviate CRD or cumulative neuropathy.

Cumulative - dose related peripheral sensory neuropathy:
Usually occurs after a cumulative dose of 800mg/m^2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approx 3 – 5 months to recovery.

Allergic reactions to oxaliplatin during infusion: Immediate intervention is to **stop the infusion** and call for medical help. Treat with IV corticosteroid and antihistamine. After full recovery, the patient may continue with folinic acid and 5FU.
At Consultant discretion, the patient may be re-challenged with oxaliplatin, according to the grade of reaction, as detailed in the separate document "Oxaliplatin Hypersensitivity & desensitisation regimen".

Dose Modifications

Haematological Toxicity:	Neutrophils < 2.0 x 10^9/l or Platelets < 100 x 10^9/l or Persistent mucositis/diarrhoea	Delay for 1 week or until completely recovered. Once recovered, use table below to determine raltitrexed dose for subsequent cycles, and continue with full dose oxaliplatin.

If toxicity does not resolve after a 3 week delay, no further treatment to be given.

Haematological Toxicity before delay	**Non–Haematological Toxicity before delay (Diarrhoea and Mucositis)**			
	Grade 0-1	**Grade 2**	**Grade 3**	**Grade 4**
Platelets ≥ 50 x 10^9/l and Neutrophils ≥ 1.0 x 10^9/l	Give 100% raltitrexed	Give 75% raltitrexed	Give 50% raltitrexed	No further treatment*
Platelets 25 – 49 x 10^9/l or Neuts 0.5 – 0.9 x 10^9/l	Give 75% raltitrexed	Give 75% raltitrexed	Give 50% raltitrexed	No further treatment*
Platelets < 25 x 10^9/l or Neutrophils < 0.5 x 10^9/l	Give 50% raltitrexed	Give 50% raltitrexed	No further treatment*	No further treatment*

Once a dose reduction has been made, all subsequent doses should be given at the reduced dose.

* Patients with this toxicity should be managed promptly with standard supportive care measures including IV hydration and bone marrow support. In addition pre-clinical data

suggest that consideration should be given to the administration of folinic acid. From clinical experience with other antifolates, folinic acid may be given at a dose of 25mg/m^2 iv every 6 hours until the resolution of symptoms.

Renal Impairment: NB. It is advised that an EDTA should be available before starting treatment, so that accurate raltitrexed dosing according to table below can be made:

CrCl (ml/min)	Raltitrexed Dose	Dose Interval
> 65ml/min	Give 100% dose	3 weekly
55-65 ml/min	Give 75% dose combined with Oxaliplatin 85mg/m^2	Raltitrexed 4 weekly Oxaliplatin 2 weekly**
25 – 54 ml/min	Give 50% dose combined with Oxaliplatin 85mg/m^2	Raltitrexed 4 weekly Oxaliplatin 2 weekly**
<25ml/min	No further treatment	N/A

Once a dose reduction has been made, all subsequent doses should be given at the reduced dose unless renal function improves.
**Scheduling as requested by Dr Middleton - all studies found have excluded patients with poor renal function, and so no data available

Hepatic Impairment: If ALT/AST > 5 x ULN or bilirubin > 10 x ULN, raltitrexed should be used with caution. There is no formal advice, but treatment using a dose reduction for raltitrexed may be considered after discussion with Consultant.

Neurological Toxicity: Grade 1 of any duration or grade 2 paraesthesias lasting longer than 7 days, continue with full-dose oxaliplatin.
Grade 2 paraesthesias persisting until next cycle; give 75% oxaliplatin dose.
Grade 3 paraesthesias lasting longer than 7 days; give 75% oxaliplatin dose.
Grade 3 paraesthesias persisting until next cycle or Grade 4 of any duration, discontinue oxaliplatin permanently.

References:
Cascinu, S et al; Ann Oncol 2002; 13: 716 – 720
Seitz, JF et al; Ann Oncol 2002; 13: 1072 – 1079
Vyzula, R et al; Neoplasma 2006; 53: 119 – 127
Popov, I et al ; Eur J Cancer 2009 ; 44 915) : 2204 – 2211 (adjuvant raltitrexed)