RALTITREXED

For use only in patients who are intolerant of 5FU or capecitabine (e.g. patients who experience coronary artery spasm), or with a contra-indication to fluoropyrimidines:

a) Advanced colorectal cancer, as an alternative to capecitabine, weekly 5FU or MdG
b) Adjuvant use in high risk Stage II, and Stage III, colon and rectal cancer, in patients also not suitable for oxaliplatin

Drug/ Dosage:	Raltitrexed	3mg/m^2 IV Day 1
Administration:	in 100ml 0.9% sodium chloride over 15 minutes	
Frequency:	advanced use:	3 weekly cycle, with review after 4 cycles
	adjuvant use:	3 weekly cycle for 8 cycles
Main Toxicities:	myelosuppression; mucositis; diarrhoea; rise in liver transaminases; ovarian failure/infertility	
Anti-emetics:	moderately emetogenic	
Extravasation:	non-vesicant	
Regular Investigations:	FBC	Day 1
	LFTs	Day 1
	U&Es	Day 1
	CEA	Day 1
	CT scan	for advanced patients, after 3 months
	EDTA	Prior to Cycle 1 (NB. Renal function predictor of toxicity – see Comments)

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.

Toxicity is increased in patients with renal impairment. Thus, strict dose modifications for renal function are necessary – see dosing advice overleaf.

Rise in transaminases 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.

Advise on good mouth care, and prescribe loperamide for management of diarrhoea.

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. Folinic acid treatment should also be considered (see Haematological Toxicity section).

Reason for Update: adjuvant use added	Approved by Consultant: Dr S Essapen
Version: 4	Approved by Lead Chemotherapy Nurse: Sarah Wills-Percy
Supersedes: Version 3	Date: 7.12.15
Prepared by: S Taylor	Checked by: C Tucker

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:

If toxicity does not resolve after 3 weeks delay, the patient is to have no further treatment.

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 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	4 weekly
25 - 54 ml/min	Give 50% dose	4 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.

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.

Reference:

Maughan, T et al; Lancet 2002; 359; 1555 – 1563
Popov, I et al; JCO 2008; 26 (15S): 4053