North West Coast
Strategic Clinical Networks

Chemotherapy Protocol

DRUG REGIMEN
Oxaliplatin and Raltitrexed

Indication for use
Metastatic colorectal adenocarcinoma and:
Unable to tolerate 5-FU (e.g. cardiac problems)
No prior chemotherapy (unless unexpected early toxicity from 5-FU based regimens)

Regimen

Raltitrexed	3mg/m^2	0.9% Sodium chloride	100ml	IV	15mins
Followed 45mins later by:					
Oxaliplatin	100mg/m^2	5% Glucose	500ml	IV	2 hours

Given every 21 days (BUT NOTE DOSE MODIFICATION CRITERIA) for 3-6 cycles

Investigation prior to initiating treatment
U&E
LFT
FBC
Baseline CEA
CT scan
Performance status 0-2

Calculated creatinine clearance
No concurrent, uncontrolled medical illness

Cautions
Avoid cold drinks for 2-3 days after Oxaliplatin infusion.

Investigations and consultations prior to each cycle
FBC, U&E, creatinine clearance
CEA every 2 cycles

The liver function test may be retrospectively looked at (i.e. after the chemotherapy treatment) **unless** they are known to be abnormal then they need to be repeated the day before so that the results are available pre-chemotherapy.

Clinic review each cycle

Side Effects
Tiredness, diarrhoea and abdominal pain, nausea and vomiting, sore mouth, poor appetite, myelosuppression and thrombocytopenia, hand foot syndrome, cardiotoxicity (including coronary artery spasm, angina and tachycardia), ocular toxicity (excessive lacrimation, visual change, photophobia), peripheral neuropathy, cold related dysaesthesia (hands/feet or laryngopharyngeal), infusion reactions, pulmonary fibrosis, veno-occlusive disease, high tone and hearing loss, ovarian failure/infertility, teratogenicity, asthenia, fever, rash, sweating, transient elevation of transaminases.

Acceptable levels for treatment to proceed (if outside these levels defer one week or contact consultant)

Creatinine Clearance >65 ml/min
Neutrophils > 1.5 x10^9/l
Platelets > 100 x10^9/l
Total bilirubin <3 ULN

ALT, AST < 2.5 ULN
Alk Phos < 2.5 ULN

If only Hb is low (below 95g/dl) please contact doctor to arrange for blood transfusion but continue with chemotherapy

Dose Modification Criteria

Renal impairment

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Creatinine clearance (ml/min)	**%Dose**	**Dosing interval**
>65	Full dose	3 weekly
55 – 65	75% dose	4 weekly
25 – 54	50% dose	4 weekly
<25	No therapy	Not applicable

Oxaliplatin

Creatinine Clearance (ml/min)	Oxaliplatin dose (%)
>50	100%
30-50	100%
<30	Omit

Hepatic impairment

Transient elevations of liver transaminase occur with raltitrexed. No dose modification is needed in mild or moderate impairment, but the liver enzymes should be monitored carefully

Raltitrexed is not recommended in severe hepatic impairment (bilirubin >10x ULN and or AST/ALT >5x ULN)

Bilirubin >3 xULN or ALT >2.5 ULN : Give 50% Oxaliplatin until liver function recovers

Cumulative dose related peripheral sensory neuropathy

Usually occurs after a cumulative dose of 800mg/m^2, and can occur after oxaliplatin has completed.

Grade1 (any duration) or grade 2 longer than 7 days	Continue oxaliplatin 100mg/m^2
Grade 2 paraesthesia persisting until next cycle	Reduce oxaliplatin to 75mg/m^2
Grade 3 paraesthesia lasting longer than 7 days	Reduce oxaliplatin to 75mg/m^2
Grade 3 paraesthesia persisting until next cycle	Discontinue oxaliplatin permanently
Grade 4 of any duration	Discontinue oxaliplatin permanently

Other 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		

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

Diarrhoea is often associated with immunosuppression so FBC must be checked in grade 3 or 4 diarrhoea.

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

This is very important and failure to make these adjustments may result in severe, even fatal, toxicity.
Repeat treatment delays weekly, to a maximum of 3 weeks, until toxicity resolves or blood count recovers fully.
If toxicity does not resolve after 3 weeks delay give no further treatment
Once a dose reduction has been made, all subsequent doses should be given at the reduced dose.

Specific Information on Administration

Folinic acid, folic acid or vitamin preparations containing these agents must not be given immediately prior to or during raltitrexed infusion.
CRO6 and PETACC trials showed an excess of treatment related mortality of raltitrexed compared to 5-FU based regimens. This was, in part, due to patients with poor renal function and this must be monitored carefully.
Patients with grade 4 GI (mucositis/diarrhoea) toxicity, or grade 3 GI toxicity with grade 4 haematological toxicity should be managed promptly with IV re-hydration and bone marrow support.
Consider folinic acid 25mg/m2 qds IV until resolution of symptoms.
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

THIS PROTOCOL HAS BEEN DIRECTED BY DR WILLIAMSON, CLINICIAN FOR COLORECTAL CANCER

RESPONSIBILITY FOR THIS TEMPLATE LIES WITH THE HEAD OF SERVICE

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