Raltitrexed in Colorectal Cancer

Indication:
1) Adjuvant therapy in Colorectal Cancer for patients intolerant to standard fluoropyrimidine with coronary artery spasm
2) Palliative therapy in Colorectal Liver Metastases for patients intolerant to standard fluoropyrimidine with coronary artery spasm

Regimen details:
Raltitrexed 3mg/m² IV D1

Administration:
Raltitrexed IV infusion in 100ml Sodium Chloride 0.9% over 15 minutes

Frequency:
Adjuvant setting: Every 21 days, for 8 cycles
Palliative setting: Every 21 days. Response should be assessed every 4 cycles and treatment continued if appropriate

Extravasation:
Raltitrexed: Non-vesicant

Anti-emetics:
Low emetogenic. Follow Local Anti-emetic Policy

Regular investigation:
FBC D1
LFTs D1
U&Es D1
CEA D1
CT scan Every 12 weeks (Palliative setting only)

DOSE MODIFICATIONS

Haematological Toxicity

Day 1
WBC < 2.0 x 10⁹/L
or
Neutrophils < 1.5 x 10⁹/L
or
Platelets < 100 x 10⁹/L

Delay for 1 week or until completely recovered
Repeat FBC – If within normal parameters, see table below:

On recovery, the dose of Raltitrexed should be reduced based upon the worst haematological toxicity experienced. Once a dose reduction has been made, all subsequent doses should be given at the reduced dose

Neutrophils (lowest observed)  Platelets  Raltitrexed Dose

≥ 1.0 x 10⁹/L AND ≥ 50 x 10⁹/L Give 100%
0.5 – 0.9 x 10⁹/L OR 25 – 49 x 10⁹/L Give 75%
< 0.5 x 10⁹/L OR < 25 x 10⁹/L Give 50% (*)

If toxicity does not resolve after 3 weeks delay, discontinue treatment
(*) If patient also develops Gastrointestinal (GI) toxicity, please see Combined GI and Haematological toxicities
Renal Impairment:

Toxicity is increased in patients with renal impairment, therefore, strict dose modifications should be followed as per table below.

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Raltitrexed Dose</th>
<th>Dose interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 65</td>
<td>Give 100%</td>
<td>Every 21 days</td>
</tr>
<tr>
<td>55 – 65</td>
<td>Give 75%</td>
<td>Every 28 days</td>
</tr>
<tr>
<td>25 – 54</td>
<td>Give 50%</td>
<td>Every 28 days</td>
</tr>
<tr>
<td>&lt; 25</td>
<td>Omit</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Hepatic Impairment:

If ALT/AST > 5 x ULN or Bilirubin > 5 x ULN (**), Raltitrexed should be used with caution and a dose reduction should be considered after discussion with Consultant

(**) Bilirubin > 5 x ULN as per Dr. Maisey recommendation

Liver transaminases rise in Cycles 2 and 3 but tend to resolve with continued treatment- it should not be interpreted as an indicator of progressive liver disease

DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

The dose reduction schemes, in Haematological and GI toxicity, should be adhered to since the potential for life threatening and fatal toxicity increases if the dose is not reduced or treatment not stopped as appropriate

Gastrointestinal toxicity

In patients with Grade 2 or 3 gastrointestinal toxicity (mucositis or diarrhoea)  See table below

In the event of any Grade 4 gastrointestinal toxicity (mucositis or diarrhoea)   Discontinue treatment  See table below

Patients who develop signs of GI toxicity should have their full blood counts monitored at least weekly for signs of Haematological toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mucositis</th>
<th>Diarrhoea</th>
<th>Raltitrexed Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Erythema of the mucosa but normal diet</td>
<td>&lt; 4 stools / day</td>
<td>Give 100%</td>
</tr>
<tr>
<td>2</td>
<td>Patchy ulcerations, can eat and swallow modified diet</td>
<td>4 – 6 stools / day</td>
<td>Give 75%</td>
</tr>
<tr>
<td>3</td>
<td>Confluent ulcerations; bleeding with minor trauma. Unable to adequately eat or hydrate orally</td>
<td>≥ 7 stools / day</td>
<td>Give 50%</td>
</tr>
<tr>
<td>4</td>
<td>Tissue necrosis; significant spontaneous bleeding Life-threatening consequences</td>
<td>Life-threatening consequences</td>
<td>Discontinue treatment</td>
</tr>
</tbody>
</table>

Once dose reduction has been made, all subsequent treatment should remain at reduced dose.
Combined Gastrointestinal and Haematological toxicities

Patients who develop signs of Grade 3 Gastrointestinal toxicity associated with Grade 4 Haematological toxicity should have their treatment stopped. Patients with such toxicity should be managed promptly with standard supportive care measures including IV hydration and bone marrow support. Consideration should be given to the administration of Folinic acid at a dose of 25mg/m² IV every 6 hours until the resolution of symptoms. Further use of Raltitrexed in such patients is not recommended.

Toxicities: Myelosuppression; nausea; vomiting; mucositis; diarrhoea; anorexia; asthenia; abdominal pain; fever; rash, sometimes associated with pruritus; fever; rise in liver transaminases

Drug interactions: Raltitrexed
-No specific interactions have been found

References:
www.medicines.org.uk
Garden OJ et al. Guidelines for resection of colorectal cancer liver metastases. 2006
SWSHCN-Raltitrexed. Approved Network regimen for Colorectal cancer. March’08
RALTITREX. CCO Formulary. Revised July 2005
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003
GSTT guidelines for treating nausea and vomiting in adult patients. September 2007
Stockley’s Drug Interactions. Interactions search: Raltitrexed. February 2009
CTCAE v3.0. August 2006