Systemic Anti Cancer Treatment Protocol

Panitumumab and FOLFIRI

PROTOCOL REF: MPHAPAFIGA
(Version No: 2.1)

Approved for use in:

Panitumumab (NICE TA439) is recommended, within its marketing authorisation, as an option for previously untreated epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer in adults in combination with:

- 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or
- 5-fluorouracil, folinic acid and irinotecan (FOLFIRI).

In some instances patients may receive ox-cap or I-cap in place of their FOLFOX or FOLFIRI when patients do not wish to have a line fitted.

Doses:

Drug	Dose	Route	Frequency
Panitumumab	6mg/kg	IV	Every 14 days
Irinotecan	180mg/m^2	IV	Every 14 days
Folinic Acid	350mg	IV	Every 14 days
Fluorouracil	400mg/m^2	IV	Every 14 days
Fluorouracil	2400mg/m^2	IV	Every 14 days

To be given for 6 cycles then review, continue until disease progression or unacceptable toxicity

Supportive treatments:

Anti-emetic risk - moderate

Aquamax® cream

Domperidone 10mg oral tablets, up to 3 times a day or as required

Dexamethasone tablets 4mg twice daily for 3 days

Loperamide 4mg immediately after first liquid stool followed by 2mg every 2 hours for at least 12 hours (maximum 16mg in 24hrs)

Extravasation risk:

Network guidelines indicate that fluorouracil and irinotecan are IRRITANTS and extravasation should be treated using Network guidance.

Contraindications include chronic inflammatory bowel disease and/or bowel obstruction

Administration:

Insertion of a PICC line is necessary to administer this regimen

Day	Drug	Dosage	Route	Diluent and Rate
1	**Dexamethasone** 30 min prior to chemotherapy	8mg	PO	
1	**Ondansetron** 30 min prior to chemotherapy	16mg	PO	
Flush with sodium chloride 0.9% before and after panitumumab				
1	**Panitumumab**	6mg/kg	IV	Infuse first dose over 60 minutes* via a 0.2 or 0.22 micrometre in-line filter. Subsequent doses can be infused over 30 - 60 minutes.
	Atropine	600 micrograms	SC	Always prior to irinotecan
1	**Irinotecan**	180 mg/m^2	IV	250mL Glucose 5% infusion over 30 to 90 minutes
1	**Folinic Acid**	350mg	IV	250mL Glucose 5% infusion over 2 hours
1	**Fluorouracil**	400mg/m^2	IV	Bolus over 5 minutes
1 to 2	**Fluorouracil**	2400mg/m^2	IV	46 hour continuous infusion in Sodium Chloride 0.9%

Cycle 1 irinotecan should be administered over 90 minutes, if tolerated this can be reduced to 60 minutes at cycle 2 and 30 mins from cycle 3 onwards.

Administer folinic acid before fluorouracil

Drug Interactions

Care with patients on coumarin anticoagulants – monitor INR closely, consider LMWH

St John's Wort – causes accelerated metabolism of irinotecan, reducing potential efficacy - avoid

Atazanavir –increased risk of toxicity of irinotecan as metabolism of irinotecan inhibited

Itraconazole – Increased risk of toxicity - avoid

Ketoconazole - Increased risk of toxicity - avoid

Lapatanib – Rarely used together seek advice from pharmacy

Sorivudine and analogues – **Potentially fatal interaction** – avoid completely

Notes:

Be aware of possible infusion related reactions with panitumumab and administer pre-meds as prescribed

Administer panitumumab before chemotherapy

Caution in patients with pre-existing neurotoxicity – see below

Caution in patients with pre-existing heart disease, angina pectoris, arrhythmias

Correct any magnesium deficiency before giving this regimen

Neutropenia with diarrhoea is a life threatening complication and requires immediate admission and management

Main Toxicities:

Panitumumab The most frequently reported adverse reactions are skin reactions and gastrointestinal disorders. Other common adverse effects include, infusion related reactions, fatigue, electrolyte disturbances, neutropenia, anaemia, mucositis, dyspnoea and/or cough, tachycardia, skin and nail changes, hair and eyelash changes, conjunctivitis, back pain.

Irinotecan Myelosuppression, diarrhoea, alopecia, cholinergic syndrome during administration, ovarian failure/infertility.

Cholinergic syndrome: Diarrhoea, sweating, blurred vision, dizziness within first 24 hours after irinotecan.

Diarrhoea: This may occur within 30-90 minutes of the infusion or may be delayed. Ensure patients are dispensed loperamide and that they know how and when to take them. Neutropenia with diarrhoea is a life threatening complication and requires immediate admission and management.

Fluorouracil Diarrhoea, nausea and vomiting, conjunctivitis / sore eyes, skin rashes, Palmar Plantar Erythema (PPE or hand foot syndrome), stomatitis, chest pain (myocardial ischaemia or angina), ovarian failure / infertility, nail ridges, taste changes
DPD deficiency – leads to severe early fluorouracil toxicity, affects approximately 3% of population, may be life threatening

Investigations and treatment plan

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing	Last cycle
Medical / Senior Nurse / AHP Assessment	X		X		X	Alternate cycles	
Nursing Assessment	X	X	X	X	X	Every cycle	Check has OPD appointment
FBC	X	X	X	X	X	Every cycle	X
U&E, LFT & Magnesium	X	X	X	X	X	Every cycle	X
Creatinine Clearance	X	X	X	X	X	Every cycle	X
Dihydropyrimidine dehydrogenase (DPD) deficiency test	X					This test is normally only required if a patient has not had capecitabine, or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result must be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. Treatment with capecitabine and fluorouracil is contraindicated in patients with known complete DPD deficiency.	
CT scan	X					Inform consultant team if not booked	Check has date for CT
Informed Consent	X						
PS recorded	X	X	X	X	X	Every cycle	X
Toxicities documented	X	X	X	X	X	Every cycle	X
Height recorded	X						
Weight recorded	X	X	X	X	X	Every cycle	X

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 if all apply:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Delay 1 week on day 1 if any apply:-

ANC ≤ 0.9 x 10^9/L	Platelets ≤ 99 x 10^9/L

If WCC, platelets or ANC (absolute neutrophil count) still below required levels for treatment at week 2, delay treatment again and reduce flourouracil and irinotecan doses by 20% for subsequent cycles. If a further delay for myelotoxicity occurs despite a 20% reduction a further 20% reduction may be considered. Refer to oncologist.

Note that panitumumab is not myelosuppressive and no dose reduction is required.

Non-haematological toxicity

<table>
<tr><td>Renal</td><td>Calculate CrCl using Cockroft and Gault formula at baseline and repeat if serum creatinine increases between cycles.
<table>
<tr><th>Creatinine Clearance (mL/min)</th><th>Irinotecan Dose</th><th>Fluorouracil Dose</th></tr>
<tr><td>≥ 30</td><td>Full dose</td><td>Full dose</td></tr>
<tr><td>< 30</td><td>Use with caution – no data</td><td>Give 75%</td></tr>
</table>
No dose adjustment required with panitumumab</td></tr>
<tr><td>Hepatic</td><td>
<table>
<tr><th>Liver function</th><th>Irinotecan dose</th><th>Fluorouracil dose</th></tr>
<tr><td>Bilirubin between 1.5 to 3 x ULN ALP>5 x ULN</td><td>50%</td><td>100%</td></tr>
<tr><td>Bilirubin > 3 x ULN</td><td>Omit</td><td>50%</td></tr>
</table>
Note that significantly impaired hepatic function might be a sign of disease progression and require cessation or change of treatment.
Always discuss deteriorating organ function with consultant</td></tr>
</table>

<table>
<tr><td colspan="2">Panitumumab</td></tr>
<tr><td>Dermatological</td><td>Treatment of dermatologic reactions should be based on severity and may include a moisturiser, sun screen (SPF > 15 UVA and UVB), and topical steroid cream (not stronger than 1% hydrocortisone) applied to affected areas, and/or oral antibiotics (e.g. doxycycline). It is also recommended that patients experiencing rash/dermatological toxicities wear sunscreen and hats and limit sun exposure as sunlight can exacerbate any skin reactions that may occur. Patients may be advised to apply moisturiser and sunscreen to face, hands, feet, neck, back and chest every morning during treatment, and to apply the topical steroid to face, hands, feet, neck, back and chest every night during treatment.

If a patient experiences an intolerable or severe skin reaction (≥ grade 3) panitumumab therapy must be interrupted. Treatment may only be resumed if the reaction has resolved to grade 2.

Recommended dose modifications for management of severe skin reactions:
<table>
<tr><td>≥ grade 3 skin reaction</td><td>Panitumumab dose after resolution to ≤ grade 2</td></tr>
<tr><td>1st occurrence</td><td>Resume at full dose</td></tr>
<tr><td>2nd occurrence</td><td>Continue at 80% of original dose</td></tr>
<tr><td>3rd occurrence</td><td>Continue at 60% of original dose</td></tr>
<tr><td>4th occurrence</td><td>Discontinue treatment</td></tr>
</table>
</td></tr>
<tr><td>Ocular</td><td>Serious cases of keratitis and ulcerative keratitis have been rarely reported in the post-marketing setting. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with panitumumab should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Panitumumab should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.</td></tr>
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Hypersensitivity reactions including anaphylaxis	If a severe or life-threatening reaction occurs during an infusion or at any time post-infusion (e.g. presence of bronchospasm, angioedema, hypotension, need for parenteral treatment, or anaphylaxis), panitumumab should be permanently discontinued. In patients experiencing a mild or moderate (CTCAE v 4.0 grades 1 and 2) infusion-related reaction the infusion rate should be reduced for the duration of that infusion. It is recommended to maintain this lower infusion rate in all subsequent infusions. Hypersensitivity reactions occurring more than 24 hours after infusion have been reported including a fatal case of angioedema that occurred more than 24 hours after the infusion. Patients should be informed of the possibility of a late onset reaction and instructed to contact their physician if symptoms of a hypersensitivity reaction occur.
Pulmonary complications	Cases of interstitial lung disease (ILD), both fatal and non-fatal, have been reported, mainly from the Japanese population. In the event of acute onset or worsening pulmonary symptoms, panitumumab treatment should be interrupted and a prompt investigation of these symptoms should occur. If ILD is diagnosed, panitumumab should be permanently discontinued and the patient should be treated appropriately. In patients with a history of interstitial pneumonitis or pulmonary fibrosis, the benefits of therapy with panitumumab versus the risk of pulmonary complications must be carefully considered.

Fluorouracil	
Chest pain, coronary artery spasm	Stop fluorouracil, standard angina investigations, refer to consultant, if symptoms persist stop permanently
Stomatitis	If mouth ulcers or > grade 2 symptoms develop treat symptomatically, delay treatment until resolved to grade 1 and reduce fluorouracil doses by 20%. See table
Diarrhoea	Treat diarrhoea between cycles symptomatically. If diarrhoea has not resolved by next cycle delay treatment by 1 week. If diarrhoea remains troublesome or more than 1 delay is required reduce both fluorouracil bolus and infusion doses by 20% and continue at the lower dose unless further toxicity occurs - See table
PPE	Treat symptomatically, delay treatment until resolved to grade 1. Reduce fluorouracil doses (bolus and infusion) by 20% for subsequent doses if persistent troublesome PPE. See table

Irinotecan	
Diarrhoea	This may be due to irinotecan and / or fluorouracil. Always treat as irinotecan induced
Diarrhoea within first 24 hours	This is likely to be caused by an acute cholinergic syndrome, do not take loperamide within the first 24 hours. Contact chemotherapy team
Delayed diarrhoea (after 24 hours post irinotecan)	Once a liquid stool occurs loperamide 4mg should be taken immediately, followed by 2mg every 2 hours for at least 12 hours, and for 12 hours following the last liquid stool. Patients should be instructed to drink large volumes of water or electrolytes. Do not continue high dose loperamide for longer than 48 hours Any concomitant fever or vomiting will require hospitalisaton for rehydration If diarrhea persists for 24 hours despite loperamide, consider ciprofloxacin 250mg BD if neutropenic (ANC ≥ 1.0 x 10^9/L) orally for 7 days If diarrhoea persists after 48 hours then patients should be hospitalised for further management and treatment review. Do **not** use loperamide prophylactically even if delayed diarrhoea occurred in previous cycles. For first episode of diarrhoea grade 1 or higher, delay treatment for 1 to 2 weeks until completely resolved and reduce dose of irinotecan in subsequent cycles by 25%. Reduce fluorouracil dose as well – see below

Fluorouracil dose reductions for non haematological toxicity

	Non haematological toxicities (diarrhoea, stomatitis, PPE)			
grade	0-1	2	3	4
1st occurrence	100%	80%	50%	Stop treatment
2nd occurrence	80%	70%	50%	Stop treatment
3rd occurrence	50%	50%	50%	Stop treatment

References:

Summary of product characteristics, Electronic Medicines Compendium, Vectibix, https://www.medicines.org.uk/emc/product/6178 [accessed on 07/06/2018]

Management of skin rash during egfr-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. Curr Oncol. 2009 Jan; 16(1): 16–26. https://www.ncbi.nlm.nih.gov/

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Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, et al. Lancet 1998;Vol 352;1407–1412

Summary of Product Characteristics,Electronic Medicines Compendium, Irinotecan, https://www.medicines.org.uk/emc/medicine/27592 [accessed on 25/06/2018]

Cetuximab and panitumumab for previously untreated metastatic colorectal cancer, NICE https://www.nice.org.uk/guidance/ta439 [accessed on 07/06/2018]