Weekly Fluorouracil and Calcium Folinate (QUASAR)

Indication
Adjuvant therapy for colorectal cancer.
First line palliative therapy for locally advanced or metastatic colorectal cancer in patients who are unsuitable for the Modified de Gramont regimen.

ICD-10 codes
Codes prefixed with C18-C20.

Regimen details

Day	Drug	Dose	Route
1	Calcium folinate	20mg/m^2	IV bolus
1	Fluorouracil	370mg/m^2	IV bolus

Cycle frequency
Weekly

Number of cycles
24 – 30 weeks depending on tolerability

Administration
Calcium folinate is administered first.
Calcium folinate followed by fluorouracil are administered by slow IV bolus via a fast running drip of sodium chloride 0.9%.

Pre-medication
Nil

Emetogenicity
This regimen has a low emetogenic potential

Additional supportive medication
Mouthwashes as per local policy.
Loperamide if required.

Extravasation
Fluorouracil is an inflammatant (Group 2)
Calcium folinate is neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
CEA	14 days

Pre-treatment investigations for subsequent cycles

Investigation	Validity period
FBC	24 hours
U+E (including creatinine)	24 hours alternate cycles only (i.e. every other week)
LFTs	24 hours alternate cycles only (i.e. every other week)
Calcium	24 hours alternate cycles only (i.e. every other week)
CEA	Monthly

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Bilirubin	< 1.5 x ULN
AST/ALT	< 3 x ULN
Creatinine Clearance (CrCl)	≥ 10mL/min

Dose modifications

- **Haematological toxicity**

Defer treatment for 1 week if neutrophil count <1.0 x 10^9/L and/or platelets <100 x 10^9/L.

- **Renal impairment**

If CrCl < 10mL/min consider dose reduction of fluorouracil (consultant decision).

- **Hepatic impairment**

Bilirubin (x ULN)		AST/ALT (x ULN)	Fluorouracil dose
< 1.5	and	≤ 1.5	100%
1.5 – 3	and	≤ 3	Consider 66% dose *
3 – 5	and	3 - 5	Consider 50% dose*
> 5	or	> 5	Contraindicated

* consultant decision

Doses may be increased up to 100% if there is no toxicity.

No dose reduction of calcium folinate is required.

- **Other toxicities**

Toxicity	Definition	Fluorouracil dose
Stomatitis/Mucositis	Grade 2	Defer until ≤ grade 1. Reduce subsequent doses to 80%.
	Grade 3	Defer until ≤ grade 1. Reduce subsequent doses to 50%.
	Grade 4	Discontinue
Diarrhoea*	Grade 2	Defer until ≤ grade 1. Reduce subsequent doses to 80%.
	Grade 3	Defer until ≤ grade 1. Reduce subsequent doses to 50% and consider prophylactic ciprofloxacin 250mg BD.
	Grade 4	Discontinue
Palmar plantar erythema (PPE)	Grade 2	Defer until ≤ grade 1. Reduce subsequent doses to 80%.
	Grade 3/4	Defer until ≤ grade 1. Reduce subsequent doses to 50%.

*Patients presenting with diarrhoea must be carefully monitored until the symptoms have resolved completely, as rapid (sometimes fatal) deterioration can occur.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Cardiac toxicity*

*Coronary artery spasm is a recognised complication of fluorouracil treatment, although the evidence base regarding aetiology, management and prognosis is not particularly strong.
Coronary artery spasm is more common in patients receiving continuous infusions of fluorouracil, and is usually reversible on discontinuing the infusion. Should a patient receiving fluorouracil present with chest pains, stop the treatment. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, the fluorouracil should be permanently discontinued.

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Diarrhoea
Stomatitis and mucositis
PPE
Alopecia
Fatigue

- **Other side effects**

Confusion

Significant drug interactions – for full details consult product literature/ reference texts

Fluorouracil:
Co-trimoxazole/trimethoprim: Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.
Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.
Allopurinol: may potentiate cytotoxic effect-avoid concomitant use
Clozapine: increased risk of agranulocytosis, avoid concomitant use
Digoxin tablets: fluorouracil may reduce digoxin absorption (give digoxin in liquid form)
Metronidazole and Cimetidine: inhibit metabolism of fluorouracil (increased exposure and risk of toxicity)
Phenytoin: reduced absorption of phenytoin.

Calcium folinate:
Anti-epileptics (phenobarbital, primidone, phenytoin): may increase the frequency of seizures.

Additional comments

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhoea and/or severe stomatitis early in the first cycle). Avoid use in patients with known DPD deficiency.

Cardiotoxicity has been associated with fluoropyrimidine therapy, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

References

- Summary of Product Characteristics calcium folinate (Hospira) accessed 7 September 2017 via www.medicines.org.uk
- Summary of Product Characteristics Fluorouracil (Hospira) accessed 7 September 2017 via www.medicines.org.uk
- Patel K., et al. Weekly 5-fluorouracil and leucovorin: achieving lower toxicity with high dose intensity in adjuvant chemotherapy after colorectal cancer resection. Ann Oncol. 2004. 15 (4): 568-573.
- QUASAR Collaborative Group. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet 2007 370 (9604): 2020-2029.

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