Modified de Gramont - fluorouracil and calcium folinate (colorectal)

Indication
Palliative therapy for stage IV or relapsed colorectal cancer.

ICD-10 codes
Codes prefixed with C18-C20.

Regimen details

Day	Drug	Dose	Route
1	Calcium folinate	350mg	IV infusion
1	Fluorouracil	400mg/m^2	IV bolus
1-2 (46 hours)	Fluorouracil	2800mg/m^2	IV infusion over 46 hours

Cycle frequency
14 days

Number of cycles
6 cycles then review. Maximum 12 cycles.

Administration
Calcium folinate is administered in 100-500mL sodium chloride 0.9% or glucose 5% over 2 hours.
Fluorouracil is administered as an IV bolus injection over 5 minutes.
Fluorouracil infusion is administered either via a central venous catheter and ambulatory infusion device over 46 hours or as a continuous peripheral IV infusion over 46 hours in 2 x 1000mL 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).

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	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Calcium	7 days

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
Creatinine Clearance (CrCl)	≥ 10mL/min

Dose modifications

- **Haematological toxicity**

Defer treatment 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 dose reduction*
3 - 5	and	3 - 5	Consider dose reduction*
> 5	or	> 5	Contraindicated

* consultant decision

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

- **Other toxicities**

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

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 14 August 2014 via www.medicines.org.uk
- Summary of Product Characteristics Fluorouracil (Hospira) accessed 14 August 2014 via www.medicines.org.uk
- Cheeseman SL, Joel SP, Chester JD, Wilson G, Dent JT, Richards FJ, Seymour MT. 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002 87(4): 393-9.
- Allwood M, Stanley A, Wright P, editors. The cytotoxics handbook. 4th ed. Radcliffe Medical Press. 2002.

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