IRINOTECAN & MODIFIED DE GRAMONT

First-line in advanced colorectal cancer (approved by NICE August 2005)
Second-line following fluoropyrimidine or oxaliplatin failure, where patient fit enough for further treatment, but irinotecan monotherapy not felt to be appropriate (not approved by NICE)

Drugs/Dosage:	Irinotecan	180 mg/m^2	IV	Day 1
	Calcium folinate (Folinic Acid)	350mg	IV	Day 1
	5-Fluorouracil	400mg/m^2	IV	Day 1
	5-Fluorouracil	2400mg/m^2	IVI over 46 hours	

Primary G-CSF prophylaxis should be considered for patients with additional risk factors – see G-CSF guidelines and / or discuss with Consultant

Administration: Irinotecan in 250ml 0.9% sodium chloride over 60 - 90 minutes
Calcium folinate in 250ml 0.9% sodium chloride over 30 minutes
5FU bolus injection over 5 minutes
5FU infusion via central venous catheter and ambulatory infusion device

Frequency: 2 weekly cycle for 6 cycles, then CT scan and clinical review
After 6 cycles, consider drug holiday in patients who have responded/stable disease, with 6 weekly clinical review and 3 monthly CT scans. Reinitiate treatment if progression seen.
N.B. This is Consultant dependent, and other options include a further 3 month block of treatment, or treatment to progression.

Main Toxicities: myelosuppression; mucositis; diarrhoea (see Comments); alopecia; cholinergic syndrome (see Comments); palmar/plantar erythema (PPE); coronary artery spasm (see Comments); ovarian failure/infertility

Anti-emetics: highly emetogenic

Extravasation: non-vesicants

Regular Investigations:	
FBC	Day 1
U&Es	Day 1
LFTs	4 weekly
CEA	4 weekly
CT scan	after 6 cycles

Comments: **Cholinergic syndrome** can be controlled by giving atropine 0.25mg subcutaneously at time of irinotecan administration. Should the syndrome develop, a further dose of atropine may be given.

Diarrhoea may occur within 30 – 90 minutes of infusion, or may be delayed. Once a liquid stool occurs, Loperamide 4mg should be taken immediately, followed by one tablet 2 hourly for at least 12 hours, and for 12 hours following the last liquid stool. Patients should be instructed to drink large volumes of water / electrolytes. Concomitant fever or vomiting will require hospitalisation for IV hydration.
If diarrhoea persists for 24 hours despite the loperamide, a prophylactic course of ciprofloxacin 250mg po bd for 7 days should be started. After 48 hours of persistent diarrhoea, the patient should be hospitalised for parenteral support and review of treatment.
Prophylactic ciprofloxacin should also be commenced in patients with neutrophils < 0.5 x 10^9/l, even in the absence of diarrhoea. Patients who develop severe neutropenia are especially at risk of infection if they are also suffering from diarrhoea.

Reason for Update: addition of statement re primary G-CSF	Approved by Consultant: Dr S Essapen
Version: 6	Approved by Lead Chemotherapy Nurse: P Deery
Supersedes: Version 5	Date: 5.6.14
Prepared by: S Taylor	Checked by: C Tucker

N.B. Loperamide and ciprofloxacin must be dispensed to patients with cycle 1, and patient should be given information leaflet and counselled to ensure they know how and when to use them.

Coronary artery spasm is a recognised complication of 5FU although the evidence base regarding aetiology, management & prognosis is not particularly strong. Coronary artery spasm is more common in patients receiving continuous infusions of 5FU, which is usually reversible on discontinuing the infusion. Should a patient receiving 5FU present with chest pains, stop the 5FU. 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 5FU should be withdrawn permanently.[1]

Dose Modifications

Haematological Toxicity:

WBC < 3.0 x 10^9/l
or
Neutrophils < 1.5 x 10^9/l
or
Platelets < 100 x 10^9/l

Delay treatment for 1 week. Repeat FBC and, if result within normal range, resume treatment.
If > 1 delay, or 1 delay of ≥ 2 weeks, reduce irinotecan & 5FU (bolus & infusion) doses by 20% for subsequent cycles.
If a further delay(s) for myelotoxicity occurs despite a 20% dose reduction, a further 20% dose reduction may be made.

Renal Impairment: Cockcroft & Gault formula may be used to predict creatinine clearance. If borderline, or if predicted renal function falls by > 30%, an EDTA should be requested.

CrCl (ml/min)	Irinotecan Dose	5 Fluorouracil Dose
< 30	Give 50% dose	Give 80% dose

Hepatic Impairment:

Liver Function	Irinotecan Dose	5 Fluorouracil Dose
Bilirubin 1. 5 –3 x ULN **or** ALP > 5 x ULN	Give 50% dose	Give 100% dose
*Bilirubin > 3x ULN	Omit irinotecan	Give 50% dose

*Bilirubin > 3 x ULN: Note that significantly impaired hepatic function may be a sign of disease progression and require cessation of, or change in, treatment. **Always discuss deteriorating organ function with consultant**.

Stomatitis: If mouth ulcers develop, reduce the 5-Fluorouracil doses (bolus and infusion) by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.

Diarrhoea: For management of diarrhoea, see "Comments" section.
If diarrhoea from the previous cycle, even if not severe, has not resolved by the time the next cycle is due, delay 1 week. If there is more than 1 delay for this reason, reduce the Irinotecan and 5FU (bolus and infusion) doses by 20% for subsequent cycles.
After an episode of severe diarrhoea (Grade 3-4), delay chemotherapy until full recovery, then reduce the Irinotecan and 5FU (bolus and infusion) doses by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.

PPE: Treat symptomatically, and initiate pyridoxine 50mg po tds. If PPE continues to be a problem, reduce the 5FU doses (bolus and infusion) by 20% for subsequent cycles.

References:
[1]COIN Guidelines Oct 2000
FOCUS trial (CR08); MRC Colorectal Cancer Group, (Protocol Version 6) January 2003