OXALIPLATIN & MODIFIED DE GRAMONT

1. First-line or subsequent use for metastatic colorectal cancer (NICE Aug 2005)
2. Adjuvant use in high risk Stage II and Stage III colon and rectal cancer
3. Second-line use in metastatic pancreatic cancer

Drugs/ Dosage:	Calcium folinate (Folinic acid)	350mg	IV	D1
	Oxaliplatin	85mg/m^2	IV	D1
	5-Fluorouracil bolus	400mg/m^2	IV	D1
	5-Fluorouracil infusion	2400mg/m^2	IVI	over 46 hours

Administration: Oxaliplatin in 250ml glucose 5% over 2 hours
concurrently with calcium folinate in 250ml glucose 5% over 2 hours
Flush with glucose 5%, and then give 5FU bolus injection over 5 minutes
5FU infusion via CVC and ambulatory infusion device over 46 hours

Frequency: 2 weekly cycle — Metastatic: 6 cycles, then CT scan and clinical review; Adjuvant crc: 12 cycles

Main Toxicities: myelosuppression; mucositis; diarrhoea; neurotoxicity (see Comments); allergic reactions (see Comments); coronary artery spasm (see Comments); palmar/plantar erythema; ovarian failure/infertility

Anti-emetics: highly emetogenic

Regular Investigations:	FBC	D1
	U&Es	D1
	Mg^{2+}	D1 (ideally, correct any low Mg^{2+} before oxaliplatin given)
	LFTs	4 weekly
	CEA	4 weekly (metastatic crc); 6-8 weekly (adjuvant crc)
	CA 19-9	4 weekly (pancreas)
	CT scan	after 6 cycles (metastatic use)

Comments: **Oxaliplatin and Neurotoxicity**

Acute Cold-related Dysaesthesia (CRD):
Many patients experience transient paraesthesia of hands & feet, and some experience laryngopharyngeal dysaesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion, and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patient should be well advised on precautions to be taken. Does not require treatment or dose reduction.
For laryngopharyngeal dysaesthesia, subsequent infusions should be given over 6 hours. Consideration to infusion of 10mmol of magnesium + 1gram of calcium gluconate in 0.9% sodium chloride 250ml over 1 hour, prior to starting the oxaliplatin, should also be made.
NB. The above management may also benefit patients who complain of pain/weakness in arm during oxaliplatin administration, but should **not** be used to try and alleviate CRD or cumulative neuropathy.

Cumulative dose related peripheral sensory neuropathy:
Usually occurs after a cumulative dose of 800mg/m^2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approx 3 – 5 months to recovery.

Allergic reactions to oxaliplatin during infusion: Immediate intervention is to stop the infusion and call for medical help. Treat with IV corticosteroid and antihistamine. After full recovery, the patient may continue with folinic acid and 5FU.
At Consultant discretion, the patient may be re-challenged with oxaliplatin, according to the grade of reaction, as detailed in the separate document "Oxaliplatin Hypersensitivity & desensitisation regimen".

Coronary artery spasm is a recognised complication of 5FU. Coronary artery spasm is more common in patients receiving continuous infusions of 5FU, and 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. Refer to Consultant.

Dose Modifications

Haematological	Neutrophils < 1.5 x 10^9/l or Platelets < 75 x 10^9/l	Delay treatment for 1 week or until FBC recovered. If any Grade 3 or 4 neutropenia (< 1.0 x 10^9/l) or thrombocytopenia (< 50 x 10^9/l) observed, reduce oxaliplatin to 65mg/m^2 (metastatic setting) or 75mg/m^2 (adjuvant) and reduce 5FU (bolus & infusion) by 20%.

Renal Impairment: Oxaliplatin may be used at 100% dose in moderate renal impairment (CrCl > 30ml/min), but monitor renal function and dose adjust according to toxicity.
If CrCl < 30ml/min, discuss with Consultant.

Hepatic Impairment[1]:

Liver Function	Oxaliplatin Dose	5 Fluorouracil Dose
*Bilirubin > 3 x ULN	Give 50% dose	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**.

Neurological Toxicity: If neurological symptoms occur, use the following oxaliplatin dose adjustment guidelines:
Symptoms lasting > 7 days and troublesome; reduce oxaliplatin dose to 65mg/m^2 (metastatic setting) or 75mg/m^2 (adjuvant setting).
Paraesthesia without functional impairment persisting until next cycle; reduce oxaliplatin dose to 65mg/m^2 (metastatic setting) or 75mg/m^2 (adjuvant setting).
Paraesthesia with functional impairment persisting until the next cycle; oxaliplatin should be discontinued. (Re-initiation may be considered if symptoms resolve)

Diarrhoea & Stomatitis: For diarrhoea or stomatitis occurring between cycles, treat symptomatically.
Further chemotherapy must be delayed until fully resolved. For any Grade 3 diarrhoea or stomatitis, reduce subsequent 5FU doses (bolus and infusion) by 20%. For any Grade 4 diarrhoea or stomatitis, or repeated Grade 3 after 5FU dose reduction, also reduce the oxaliplatin to 65mg/m^2 (metastatic setting) or 75mg/m^2 (adjuvant setting) for subsequent cycles.

Palmar/Plantar Erythema: Treat symptomatically, initially with pyridoxine 50mg po tds. If Grade 3 or 4 PPE occurs, delay further treatment until Grade 0 – 1 and then reduce the 5FU (bolus and infusion) by 20% for subsequent cycles.

References:
[1]MRC Colorectal Cancer Group; FOCUS Trial (CR08), January 2003 (metastatic crc)
International Journal of Palliative Nursing, 2001, Vol 7, No 7
Andre, T et al; NEJM 2004; 350 (23): 2343 – 2351 (adjuvant crc)
Tsavaris et al; Invest New Drugs 2005; 23 (4): 369-375 (pancreas)