Chemotherapy Protocol

GYNAECOLOGICAL CANCER

IRINOTECAN-MITOMYCIN

Regimen

- Ovary-Irinotecan-Mitomycin

Indication

- Platinum refractory clear cell or mucinous ovarian cancer
- Recurrent platinum-resistant, taxane-resistant ovarian cancer where other treatments are inappropriate
- WHO performance status 0, 1, 2
- Palliative intent.

Toxicity

Drug	Adverse Effect
Irinotecan	Acute cholinergic syndrome, diarrhoea (may be delayed)
Mitomycin	Nephrotoxicity, myelosuppression (cumulative)

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFTs and U&Es prior to day each cycle
- CA125 prior to each cycle

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Prior to each cycle the following criteria must be met;

Criteria	Eligible Level
Neutrophil	equal to or more than $1.5x10^9$/L
Platelets	equal to or more than $100x10^9$/L

Day 1

Neutrophils ($x10^9$/L)	Dose Modifications (irinotecan and mitomycin)
1.5 or greater	100%
less than1.5	Delay one week. If the neutrophils recover to $1.5x10^9$/L or greater at this point continue with full dose. If still less than $1.5x10^9$/L delay a further week. If recovery occurs at this point continue with 80% of the dose of both agents
Platelets ($x10^9$/L)	**Dose Modifications**
100 or greater	100%
50 - 99	Delay one week. If the platelets recover to $100x10^9$/L or greater at this point continue with full dose. If they are still less than $100x10^9$/L delay a further week. If recovery occurs at this point continue with 80% of the dose of both agents
less than 50	Delay until recovery to $100x10^9$/L or greater then continue with 50% of the dose

Day 15

Neutrophils ($x10^9$/L)	Dose Modifications (irinotecan and mitomycin)
1 or greater	100%
0.5 - 1	80%
less than 0.5	omit
Platelets ($x10^9$/L)	**Dose Modifications**
100 or greater	100%
50 - 100	80%
less than 50	omit

Consider omitting the day 15 mitomycin for future cycles if repeated delays due to immunosuppression are required.

Hepatic Impairment

Drug	Bilirubin (µmol/L)		AST/ALT units	Dose
Irinotecan	1.5xULN or greater		5xULN or greater	Not Recommended
Mitomycin			2xULN or greater	Clinical decision

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Irinotecan	N/A	No dose adjustment needed
Mitomycin	60 or greater	100%
	10-60	75%
	less than 10	Contra-indicated

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent should then be reduced to 80% of the original dose or discontinued as appropriate.

Irinotecan

Irinotecan is associated with a number of toxic reactions. The next cycle of treatment should not be administered until all toxicities have resolved to 0 or 1 of the National Cancer Institute Common Toxicity Criteria scale (NCI-CTC). Diarrhoea must have resolved completely. Where a NCI-CTC grade 3 or above event has occurred the irinotecan dose must be reduced to 80% of the original dose.

Regimen

28 day cycle for 6 cycles

Drug	Dose	Days	Administration
Irinotecan	120mg/m^2	1, 15	Intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes
Mitomycin	7mg/m^2	1	Intravenous bolus over 10 minutes

Dose Information

- Irinotecan will be dose banded according to the CSCCN agreed bands.
- Mitomycin dose will be rounded to the nearest 1mg (up if halfway)

Administration Information

Extravasation

- Irinotecan - irritant
- Mitomycin - vesicant

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy

  - dexamethasone 8mg oral or intravenous
  - ondansetron 8mg oral or intravenous

  As take home medication

  - dexamethasone 4mg oral twice a day for 3 days
  - metoclopramide 10mg oral three times a day as required

- Subcutaneous atropine 0.25mg immediately prior to irinotecan and then when required for the relief of acute cholinergic syndrome.
- Oral loperamide 4mg initially then 2mg every two hours once first liquid stool appears and continue until 12 hours after the last liquid stool. Do not use for longer than 48 hours.
- Consider oral ciprofloxacin 500mg twice daily where diarrhoea continues for more than 24 hours. Review the patient before starting this treatment.
- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Coding (OPCS 4.6)

- Procurement – X70.8 (Unspecified)
- Delivery – X72.9 (Unspecified) & X72.4

References
1.Shimizu Y, Umezawa S, Hasumi K. A phase II study of combined CPT-11 and mitomycin-C in platinum refractory clear cell and mucinous ovarian carcinoma. Ann Acad Med Singap 1998;27:650–656.
Tanaka H, Umekawa T, Nagao K et al. Salvage chemotherapy with a combination of irinotecan hydrochloride and mitomycin C in platinum- and paclitaxel-resistant epithelial ovarian cancer: case reports. Eur J Gynaecol Oncol. 2003; 24 (3-4): 337-40.

REGIMEN SUMMARY

Irinotecan-Mitomycin

Day 1

1. Atropine sulphate 250mcg subcutaneous for the prevention of irinotecan induced cholinergic effects

2. Dexamethasone 8mg oral or intravenous

3. Ondansetron 8mg oral or intravenous

4. Mitomycin 7mg/m^2 intravenous bolus over 10 minutes.

5. Irinotecan 120mg/m^2 in 250ml sodium chloride 0.9% intravenous infusion over 90 minutes.

6. Atropine Sulphate 250mcg subcutaneous when required for the relief of irinotecan induced cholinergic effects

Take Home Medicines

7. Dexamethasone 4mg oral twice a day for 3 days starting the day after chemotherapy (day 2 and 16)
   Administration Instructions
   Please supply sufficient quantity for days 1 and 15 of the cycle

8. Metoclopramide 10mg oral three times a day for 3 days then 10mg three times a day when required for nausea
   Administration Instructions
   Please supply 60 tables or nearest appropriate equivalent

Day 15

9. Atropine sulphate 250mcg subcutaneous for the prevention of irinotecan induced cholinergic effects

10. Dexamethasone 8mg oral or intravenous

11. Ondansetron 8mg oral or intravenous

12. Irinotecan 120mg/m^2 in 250ml sodium chloride 0.9% intravenous infusion over 90 minutes.

13. Atropine Sulphate 250mcg subcutaneous when required for the relief of irinotecan induced cholinergic effects

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	June 2014	Atropine instructions clarified	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	April 2014	Bolus removed from intravenous bolus throughout text Metoclopramide dose changed to 10mg from 10-20mg Atropine added as a standard pre-treatment to irinotecan Dexamethasone take home clarified Disclaimer updated	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1	May 2013	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr Clare Green Consultant Medical Oncologist Dr Cheng Yeoh Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospital NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.