**Systemic Anti Cancer Treatment Protocol**

# Paclitaxel
# Gynaecological Cancer

**PROTOCOL REF: MPHAGYNPAC**
**(Version No: 1.2)**

## Approved for use in:

- Second/ third line option for advanced ovarian cancers (weekly regimen).
- Metastatic endometrial carcinoma (weekly regimen)
- Metastatic cervical carcinoma (3 weekly or weekly regimen)
- Metastatic squamous cell carcinoma of the vulva (weekly regimen)

## Dosage

**3-weekly regimen for cervical cancer only**

| Drug | Dose | Route | Frequency |
|---|---|---|---|
| **Paclitaxel** | **135mg/m$^2$** | IV Infusion | 21 day cycles, max. 6 cycles |

**Weekly regimen**

| Drug | Dose | Route | Frequency |
|---|---|---|---|
| **Paclitaxel** | **80mg/m$^2$** | IV Infusion | Days 1,8 and 15 of a 28 day cycle, until disease progression |

**Supportive Treatments:**

Domperidone 10mg tablets, three times a day when required

## Interactions

**Antiepileptics (CYP 3A4 inducers)**

Carboplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages. Phenytoin, carbamezapine and phenobarbital increase the clearance of paclitaxel and increase its maximum tolerated dose.

**Ciclosporin**

Levels of paclitaxel increased after oral administration of ciclosporin.

**Fluconazole/Ketoconazole (CYP3A4 inhibitors)**

Paclitaxel levels may be increased

**Quinine and Verapamil**

Paclitaxel levels possibly increased.

## Extravasation risk:

Paclitaxel - vesicant.

## Administration

**3 weekly regimen for cervical cancer only**

| Day | Drug | Dose | Route | Diluent and rate |
|---|---|---|---|---|
| 1 | Dexamethasone | 20mg | IV bolus | 30 minutes before chemotherapy |
| 1 | Famotidine | 20mg | Oral | At least 60 minutes before paclitaxel (can be discontinued after three cycles for those patients who do not experience a drug hypersensitivity reaction) |
| 1 | Chlorphenamine | 10mg | IV bolus | 30 minutes before paclitaxel |
| 1 | **Paclitaxel** | **135mg/m$^2$** | **IV Infusion** | **500mL sodium chloride 0.9% over 3 hours** |

**Weekly regimen**

| Days | Drug | Dose | Route | Diluent and rate |
|---|---|---|---|---|
| 1,8,15 | Dexamethasone | 8mg (reduce to 4mg for week 2) | IV bolus | 30 minutes before chemotherapy |
| 1,8,15 | Famotidine | 20mg | Oral | At least 60 minutes before paclitaxel (can be discontinued after three cycles for those patients |

| | | | | |
|---|---|---|---|---|
| | | | | who do not experience a drug hypersensitivity reaction) |
| 1,8,15 | Chlorphenamine | 10mg | IV bolus | 30 minutes before chemotherapy |
| 1,8,15 | **Paclitaxel** | **80mg/m$^2$** | **IV Infusion** | **250mL sodium chloride 0.9% over 60 minutes** |

- Paclitaxel must be administered using a non-PVC giving set with a 0.22 micron filter.
- Paclitaxel in solution may show haziness which is attributed to the formulation of paclitaxel.
- Excessive shaking, agitation, or vibration of paclitaxel may induce precipitation and should be avoided
- Premedication treatment of chlorphenamine, dexamethasone and famotidine is given prior to paclitaxel to reduce the risk of hypersensitivity. Paclitaxel reactions commonly occur within the first few minutes of starting the infusion most likely with the first two cycles. Carboplatin risk of hypersensitivity and anaphylaxis may increase with previous exposure to platinum therapy.
- Famotidine can be stopped after three cycles for those patients who do not experience a drug hypersensitivity reaction.

## Hypersensitivity

As with all paclitaxel based chemotherapy, patients may experience allergic reaction during administration. The infusion should be stopped and the following should be administered.

- Hydrocortisone 100 to 200mg IV
- Chlorphenamine 10 mg IV

Refer to the Trusts Hypersensitivity Guidelines for further information.

**It should be strongly noted that patients who have severe reactions should not be re-challenged**

## Main Toxicities

| | |
|---|---|
| **Haematological** | Neutropenia, anaemia, thrombocytopenia, |
| **Cardiac and Vascular disorders** | Risk of bradycardia and hypotension is common |
| **Gastrointestinal** | Nausea, vomiting, diarrhoea, constipation, mucositis |
| **Musculoskeletal** | Arthralgia, myalgia |
| **Nervous system** | Paclitaxel: peripheral neuropathy is very common |
| **Hepatobiliary** | Elevation of liver transaminases, alkaline phosphatase and bilirubin. |
| **Skin and subcutaneous tissue disorders** | Alopecia<br>Allergic skin rash frequently associated with pruritus |
| **General disorders and administration site conditions** | Malaise, fever, chills, urticaria, flu-like syndrome, rash, pruritus.<br><br>Injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis) |

.

## Investigations

| | Pre | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 | Ongoing |
|---|---|---|---|---|---|---|---|---|
| Medical Assessment | X | | | | X | | | After cycles 3 and 6 then as per management plan |
| SACT Assessment | X | X | X | X | X | X | X | Every cycle |
| FBC | X | X | X | X | X | X | X | Every cycle |
| U&E & LFT | X | X | X | X | X | X | X | Every cycle |
| CrCl | X | X | X | X | X | X | X | Every cycle |
| CA125* | X | X | X | X | X | X | X | Every cycle<br>*For ovarian patients only |
| CT scan | X | | | | X | | | After 3 and 6 cycles |
| Informed Consent | X | | | | | | | |
| PS recorded | X | X | X | X | X | X | X | Every cycle |
| Toxicities documented | X | X | X | X | X | X | X | Every cycle |
| Weight recorded | X | X | X | X | X | X | X | Every cycle |

## Dose Modifications and Toxicity Management:

### Haematological Toxicity

Proceed on day 1 if-

| | |
|---|---|
| Plt ≥ 100 x $10^9$/L | ANC ≥ 1.0 x $10^9$/L |

Delay 1 week on day 1 if-

| | |
|---|---|
| Plt ≤ 99 x $10^9$/L | ANC ≤ 0.9 x $10^9$/L |

Proceed on day 8 and day 15 of weekly regimen if:

| | |
|---|---|
| Plt ≥ 100 x $10^9$/L | ANC ≥ 1.0 x $10^9$/L |

Omit day 8 or day 15 if toxicity occurs – do not delay

### Non-haematological Toxicity

**Grading and Management of Toxicity**

Toxicity should be grading according to the CTCAE v4.0 criteria. Following assessment treatment should be withheld for any toxicity until resolved to grade 0/1. For dose modification, follow the general guidance below and discuss with treating clinician.

| | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|
| **1st appearance** | Interrupt treatment until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis where possible | Interrupt treatment until resolved to grade 0/1, then continue at 75-80% of original dose | Discontinue treatment |
| **2nd appearance** | Interrupt treatment until resolved to grade 0/1, then continue at 75-80% of original dose | Interrupt treatment until resolved to grade0/1, then continue at 50% of original dose | |
| **3rd appearance** | Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose | Discontinue treatment | |
| **4th appearance** | Discontinue treatment | | |

## Peripheral Neuropathy

| **Paclitaxel** |
|---|
| CTCAE grade 2 peripheral neuropathy: withhold paclitaxel until the neuropathy recovers to grade 1 then dose reduce to 75% of the original dose. Where the peripheral neuropathy is ≥grade 3 omit further paclitaxel. |

## Hepatic Impairment

**Paclitaxel**

| **Bilirubin /µmol/l** | **Dose in mg/m²** |
|---|---|
| < 26 | 135 |
| 27-51 | 75 |
| >51 | 50 |

Patients with severe hepatic impairment must not be treated with paclitaxel.

Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. There is no evidence that the toxicity of paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. No data are available for patients with severe baseline cholestasis.
Patients should be monitored closely for the development of profound myelosuppression.

If bilirubin < 1.25 x ULN and transaminase < 10 x ULN, dose at 100%

## Renal Impairment

No dose reductions necessary.

## References

www.medicines.org.uk

Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009)

Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009)

Stockley's drug interactions. Ninth edition. Edited K. Baxter. Pharmaceutical press. London. 2010

Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum based chemotherapy: a Gynaecologic Oncology Group study

Markman et al

J Clin Oncol 1994 12:1748-1753

Phase II trial of weekly single agent paclitaxel in platinum/paclitaxel refractory ovarian cancer

Markman et al

J Clin Oncol 2002 20(9):2365-2369