Kent and Medway Cancer Collaborative

Oncological Treatment of Gynaecological Cancer

Pathway of Care

Kent & Medway Cancer Collaborative

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1.0 INTRODUCTION

- This document has been written to provide guidance on the treatment of Gynaecological cancer in the Kent & Medway Cancer Collaborative (KMCC).
- Radiotherapy schedules are as defined in the Kent Oncology Centre Quality System Clinical Protocols. For details regarding indications for radiotherapy in gynaecological cancers, please see disease orientated group Pathway of Care (PoC) documents located on the KMCC website: www.KMCC.nhs.uk.
- See network chemotherapy prescribing proformas for details of chemotherapy / anti-cancer regimens.
- All patients will be considered for entry into a clinical trial where appropriate (see appendix B).
- All patients should be discussed within a multidisciplinary team meeting before commencing initial treatment.
- At referral the following information is essential:
    - Histological / cytological confirmation of diagnosis.
    - The extent of local, nodal and metastatic disease.
    - Consider the age and general condition of the patient.
- All chemotherapy regimens listed within this document are delivered at either Maidstone and Tunbridge Wells NHS Trust or East Kent Hospitals University NHS Foundation Trust or Darent Valley Hospital.
- Please note, some of the drugs/doses recommended within this document are outside of the U.K. licensed marketing authorisation.
- To allow for flexibility in the management of cancer during the COVID-19 pandemic, NHS England has endorsed interim treatment regimens for some cancer medicines. This is to reduce the need for direct patient contact for administration of drugs and to minimise potential side effects that make people more susceptible to viral infections and other ill-health effects that may add pressure to the health system. These interim treatment regimens can be access here:

https://www.nice.org.uk/guidance/ng161/chapter/7-Modifications-to-usual-service#interim-nhs-england-treatment-regimens

2.0 OVARY

2.1 Epithelial Ovarian Carcinoma and Carcinosarcoma

- Serous adenocarcinoma (SnoMED M84413)
- Endometrioid adenocarcinoma (SnoMED M83803)
- Clear cell adenocarcinoma (SnoMED M83103)
- Mucinous adenocarcinoma (SnoMED M84803)
- Ovarian adenocarcinoma NOS (SnoMED M81403)
- Carcinosarcoma (malignant mesodermal mixed tumour) (SnoMED M89503)

2.1.1 Treatment by Stage

Borderline tumours Invasive disease	Surgery
Ia/bGI/2	• Surgery • Consider adjuvant chemotherapy if sub-optimally staged
Ia/bG3.Ic.2a	• Surgery • Adjuvant chemotherapy
2b.3.4	• Surgery if appropriate (either as initial therapy or as a deferred debulking procedure following initial chemotherapy) • Chemotherapy

N.B. Epithelial ovarian tumours of borderline malignancy should not be considered routinely for chemotherapy treatment.

2.1.2 Chemotherapy

2.1.2.1 Adjuvant / First Line Treatment of Ovarian Cancer

Patients who undergo primary cytoreductive surgery will be referred to an oncologist for consideration of post-operative chemotherapy. This will be either in the adjuvant setting for patients with early ovarian cancer with high risk factors for recurrence or as treatment for patients with advanced ovarian cancer.

Indications

All patients need to be adequately staged for consideration of chemotherapy.

Patients with sub optimal staging may be offered chemotherapy at the clinician's discretion.

Adequately staged patients with stages IAG1, IAG2, IBG1 and IBG2 should NOT be offered chemotherapy.

All other patients should be considered for chemotherapy treatment.

A)	**Patients of poorer performance status (2-3) / co-morbidity / unwilling to consider the additional toxicity of combination chemotherapy / majority of patients with stage I disease:**
	• Carboplatin AUC5 (AUC6 if based on Cockcroft Gault formula) x 6 cycles
B)	**Patients of good performance status (0-1):**

	• Combination chemotherapy with Carboplatin AUC5 (AUC6 if based on Cockcroft Gault formula) and paclitaxel 175 mg/m^2 x 6-8 cycles
	• Consider adding bevacizumab at a dose of 7.5mg/kg (see prescription proforma) at cycle 1 or 2 of chemotherapy followed by maintenance bevacizumab (funding approval required) in the following patient groups:
	  ○ Following up front surgery for FIGO stage 3C sub optimally de-bulked with residual disease >1cm
	  ○ For all patients with FIGO stage 4 disease
	  ○ For inoperable disease

NB: Carboplatin may be dosed at AUC5 based on Cockcroft Gault formula at clinician's discretion.

2.1.2.2 Maintenance Treatment Following First Line Chemotherapy

Olaparib tablets for maintenance treatment in patients with a BRCA mutation high grade epithelial (serous or endometrioid) stage III or IV ovarian, fallopian tube or primary peritoneal carcinoma who are in response following a minimum of 4 cycles of platinum-based first line chemotherapy; treatment should be started within 8 weeks.

Niraparib for maintenance treatment in patients with high grade epithelial stage III or IV ovarian, fallopian tube or primary peritoneal carcinoma who are in response following a minimum of 4 cycles of platinum-based FIRST line chemotherapy; treatment should be started within 12 weeks.

Olaparib in combination with bevacizumab as maintenance treatment in patients with high grade epithelial stage III or IV ovarian, fallopian tube or primary peritoneal carcinoma who are in response following platinum-based first line chemotherapy AND whose cancer has a positive status for homologous recombination deficiency as defined by the presence of either a deleterious or suspected deleterious BRCA 1/2 germline and/or somatic mutation or genomic instability.

2.1.2.3 Letrozole after First Line Chemotherapy

Low grade serous ovarian tumours WITH persistent/residual disease that has responded to first line chemotherapy should be started on letrozole. A baseline DEXA is recommended.

2.1.2.4 Neo Adjuvant Chemotherapy for Ovarian Cancer

Patients who are considered unsuitable for primary surgery due to disease parameters will be considered for neo adjuvant chemotherapy. Deferred debulking surgery should be considered after 3 to 4 cycles of chemotherapy.

- Carboplatin AUC5 (AUC6 if based on Cockcroft Gault formula) and paclitaxel 175 mg/m^2 x 6-8 cycles
- Consider adding bevacizumab at a dose of 7.5mg/kg (see prescription proforma) after interval debulking surgery at cycle 1 or 2 post-operative, followed by maintenance bevacizumab (funding approval required) in the following circumstances:
  - FIGO stage 3C sub optimally de-bulked with residual disease >1cm
  - Patients who had FIGO stage 4 disease at presentation
  - Patients who have inoperable disease

N.B. Carboplatin may be dosed at AUC5 based on Cockcroft Gault formula at clinician's discretion.

2.1.2.5 Second and Subsequent Line Chemotherapy

1)	**Platinum-sensitive disease** (patients relapsing greater than 6 months after completing primary chemotherapy):
	Within this group, patients with a greater than 12 month interval between completion of previous platinum-containing chemotherapy and clinical evidence of disease relapse are considered platinum sensitive and those with a 6-12 month interval are considered partially platinum sensitive.
a)	**Patients of poorer performance status (2-3) or excessive toxicity with prior combination chemotherapy:**
	• Carboplatin AUC5 (AUC6 if based on Cockcroft Gault formula) x 6 cycles
b)	**Patients of good performance status (0-1):**
	• Consider combination chemotherapy with Carboplatin AUC5 (AUC6 if based on Cockcroft Gault formula) and Paclitaxel 175 mg/m^2 x 6 cycles NB: Carboplatin may be dosed at AUC5 based on Cockcroft Gault formula at clinician's discretion • Patients with residual neuropathy (or patient preference) may be considered for combination chemotherapy with: **First choice:** • Pegylated liposomal doxorubicin (Caelyx) 30mg/m^2 and Carboplatin AUC 5 both given on day 1 every 4 weeks for 6 cycles. • Consider adding bevacizumab at a dose of 15mg/kg with each chemotherapy cycle, and as maintenance therapy until disease progression for patients not previously treated with bevacizumab or other anti-VEGF treatment (not funded within the NHS). • Carboplatin AUC5 (AUC6 if based on Cockcroft Gault formula) x 6 cycles • Carboplatin AUC 4 day 1 and Gemcitabine 1000mg/m^2 days 1 and 8 every 21 days x 6.
c)	**Patients previously intolerant of Carboplatin:**

	• Consider alternative platinum agent (e.g. Cisplatin 60-75 mg/m^2 IV every 3 weeks) • Consider Carboplatin desensitization***** • Paclitaxel 175 mg/m^2 IV every 3 weeks x 6 cycles • Paclitaxel 80 mg/m^2 IV weekly for 18 weeks • Caelyx 40-50 mg/m^2 IV every 4 weeks x 6 cycles • Myocet 60mg/m^2 IV every 4 weeks x6 cycles in place of Caelyx (only during period where Caelyx is unavailable) Choice of agent / regimen may be determined by prior Taxane exposure, performance status and toxicity considerations.
	*** Carboplatin Desensitisation** Patients should be counselled regarding the risk of further hypersensitivity reactions to carboplatin, including the possibility of anaphylaxis, and alternative treatment options also discussed. Patients should be asked to provide written informed consent to proceed with Carboplatin desensitisation. In the event of a hypersensitivity reaction occurring, the following must be documented and communicated **i.** The step at which the hypersensitivity reaction occurred **ii.** The symptoms experienced by the patient **iii.** The treatment administered for the hypersensitivity reaction and the response to treatment **iv.** The tolerance of the remaining infusion **v.** If a further hypersensitivity reaction occurred, the same information in i-iv should be documented for the second occurrence
d)	**Maintenance treatment**
	The following may be considered if the patient has not previously received a PARP inhibitor. **Niraparib or rucaparib** should be considered as maintenance treatment in patients with relapsed, platinum-sensitive and high grade serous ovarian, fallopian tube or primary peritoneal carcinoma who are: • In response following platinum-based SECOND line (or second or subsequent line for rucaparib) chemotherapy with PS 0-1 and have a known germline BRCA 1 or 2 mutation. **OR** • In response following platinum-based SECOND or SUBSEQUENT line chemotherapy with PS 0-1 and who do not have a germline BRCA mutation (i.e. have been tested and are germline BRCA 1 and 2 wildtype). **Olaparib tablets** should be considered for patients with platinum sensitive (either complete or partial response), relapsed BRCA –mutated disease as maintenance therapy. following response to 2nd, 3rd or subsequent line platinum-based chemotherapy.

2)	**Platinum-resistant disease** (patients relapsing within 6 months of completing their primary chemotherapy):
	Within this group, patients with a response to the previous platinum-based therapy but clinical evidence of disease relapse within 6 months of completion are considered platinum resistant and those with progression during their previous platinum-based therapy are considered platinum refractory.
a)	**No prior Taxane:**
	• Paclitaxel 175 mg/m^2 x 6 cycles • Paclitaxel 80 mg/m^2 weekly for 18 weeks
b)	**Prior Taxane or unsuitable for Taxane:**
	• Caelyx 40 – 50 mg/m^2 every 4 weeks x 6 cycles • Myocet 60mg/m^2 IV every 4 weeks x 6 cycles in place of Caelyx (only during period where Caelyx is unavailable). • Paclitaxel 80 mg/m2 weekly for 18 weeks

Subsequent lines of treatment:

- Weekly Carboplatin AUC 2 for 18 weeks
- Carboplatin given every 3 weeks with weekly paclitaxel (off protocol)
- In selected patients, consider single agent gemcitabine or gemcitabine and carboplatin.
- Hormonal treatment for ER+ive patients - aromatase inhibitor (preferred) or tamoxifen, prolongs the chemotherapy free interval, to be used at relapse following any line of therapy or when a patient is not suitable for chemotherapy (at any other point).

2.1.2.6 Overview of PARP Inhibitors for Ovarian Cancer

	Maintenance following 1st line chemo	Maintenance following 2nd line chemo	Maintenance following 3rd / subsequent line	Number of weeks within which treatment must be started (see BT form)	Treatment duration	Comments (additional form)
BRCA Mutation						
Olaparib	✔	✔	✔	8	<u>Maintenance following 1st line:</u> Until PD / toxicity / choice or for 2 years if the patient is in complete remission at that point. <u>Maintenance following 2nd, 3rd or subsequent line:</u> Until PD / toxicity / choice	<u>Maintenance following first line:</u> For patients with stable residual disease after 2 years, treatment may continue after completion of Blueteq form OLAP1b.
Olaparib in combination with bevacizumab	✔			9	Until PD/ toxicity / choice or for a maximum total treatment duration of 2 years	Maximum bevacizumab treatment duration is 15 calendar months (from the start of bevacizumab-containing treatment, whether this was with chemotherapy or as maintenance therapy).
Niraparib	✔			12	Until PD/ toxicity / choice Note: may be discontinued after approximately 3 years of maintenance treatment after discussion between clinician and patient.	
Niraparib		✔		8	Until PD / toxicity / choice	
Rucaparib		✔	✔	8	Until PD / toxicity / choice	
No BRCA mutation & HRD -ve / HRD unknown						
Niraparib	✔			12	Until PD/ toxicity / choice Note: may be discontinued after approximately 3 years of maintenance treatment after discussion between clinician and patient.	
Niraparib		✔	✔	8	Until PD / toxicity / choice	
Rucaparib		✔	✔	8	Until PD / toxicity / choice	

No BRCA mutation & HRD +ve						
Olaparib in combination with bevacizumab Myriad test with genomic instability score of >= 42	✔			9	Until PD/ toxicity / choice or for a maximum total treatment duration of 2 years	Maximum bevacizumab treatment duration is 15 calendar months (from the start of bevacizumab-containing treatment, whether this was with chemotherapy or as maintenance therapy).
Niraparib	✔			12	Until PD/ toxicity / choice Note: may be discontinued after approximately 3 years of maintenance treatment after discussion between clinician and patient.	
Niraparib		✔	✔	8	Until PD / toxicity / choice	
Rucaparib		✔	✔	8	Until PD / toxicity / choice	

2.2 Sex Cord Stromal Tumours

- Adult Granulosa Cell tumours
- Sertoli-Leydig tumours
- Juvenile Granulosa Cell tumours

After appropriate cytoreductive surgery, there is little data upon which to base treatment decisions. In recurrent disease where further surgery is not possible, patients may be offered high dose progestogens or aromatase inhibitors or alternatively palliative radiotherapy. Chemotherapy with single agent platinum or platinum combinations may be considered.

2.2.1 First line / Adjuvant Chemotherapy

2.2.1.1 Indications:

(a) Post-Operative:	FIGO stage II-IV
(b) Initial Therapy:	Clinical stage III-IV Consider deferred debulking surgery after 3 - 4 cycles

2.2.1.2 Treatment

Activity has been reported with Bleomycin, Etoposide and Cisplatin (BEP) combination chemotherapy. Platinum/ Taxane combinations also appear active, with less toxicity than BEP.

2.2.2 Recurrent Chemotherapy Naïve Disease

Where possible surgical resection of recurrent disease should be considered. Chemotherapy with BEP, single agent platinum or platinum / Taxane combination may provide palliative benefit.

2.3 Germ Cell Tumours

Patients are referred to Charing Cross for a Supraregional opinion after appropriate radiological and surgical staging.

2.4 Small Cell Ovarian Cancer

2.4.1 Palliative

Chemotherapy:

- Carboplatin AUC 5 day 1 and Etoposide 100mg/2 iv day 1 Etoposide orally 200mg/m2 days 2 and 3 every 21 days x 6 cycles

3.0 CERVIX

3.1 Radical Treatment for Cervical Cancer

Patients with potentially curable disease not suitable for or do not want radical surgery:

- Consider radical chemoradiotherapy using concurrent Cisplatin 40mg/m2 maximum 80mg every week for 5 weeks
- Consider radical radiotherapy alone if patient unsuitable for chemotherapy

3.2 Neo-Adjuvant Treatment

- Whilst the standard approach for cervical patients suitable for radical treatment remains chemoradiotherapy, for patients who are borderline suitable for chemoradiotherapy, consider neo-adjuvant chemotherapy prior to chemoradiotherapy with paclitaxel 80mg/m2 (capped at 160mg) and carboplatin AUC 2 (capped at 270mg), both given weekly for 6 weeks.

3.3 Adjuvant Treatment

Patients who have undergone radical surgery with risk factors for recurrence or patients with unexpected cervical cancer after hysterectomy:

- Consider adjuvant radiotherapy with or without concurrent Cisplatin 40mg/m2 maximum 80mg every week for 5 weeks
- Adjuvant vaginal vault brachytherapy should be considered after external beam radiotherapy for patients with close or involved vaginal margins.

3.4 Palliative Treatment

3.4.1 Disease limited to the pelvis but not suitable for radical treatment

- Consider palliative radiotherapy

3.4.2 Disease outside the pelvis

- Consider palliative chemotherapy
- Patients with persisting focal symptoms will also be considered for palliative radiotherapy
- Patients with recurrent and subsequent metastatic disease who are not considered suitable for surgical salvage will also be considered for palliative chemotherapy.

3.4.2.1 Chemotherapy

A)	**First line**
	• Bevacizumab 15mg/kg every 3 weeks given with paclitaxel and either cisplatin or carboplatin for primary stage IVB, recurrent, or persistent disease not amenable to curative treatment with surgery and/or radiotherapy (funding approval required). • Carboplatin AUC5 (AUC6 if based on Cockcroft Gault formula) and Paclitaxel 175mg/m^2 every 21 days x 6 cycles NB: Carboplatin may be dosed at AUC5 based on Cockcroft Gault formula at clinician's discretion • Cisplatin 50mg/m^2 x 6 cycles . • If cisplatin naïve, Topotecan 0.75mg/m^2/day days 1-3 and Cisplatin 50mg/m^2 day 1 every 21 days x 6 cycles may be considered in stage IVB or recurrent cervical cancer.
B)	**Second line**
	• Topotecan 0.75mg/m^2/day days 1-3 and Cisplatin 50mg/m^2 day 1 every 21 days x 6 cycles • Cisplatin 50mg/m^2 x 6 cycles

3.5 Small Cell Cervical Cancer

3.5.1 Neo Adjuvant

Chemotherapy:

- EP (Etoposide 100mg/m^2 iv days 1 to 3 and Cisplatin 75mg/m^2 day 1) every 21 days x 4 cycles with GCSF
  Followed by chemoradiotherapy with weekly Cisplatin 40mg/m^2 maximum 80mg every week for 5 weeks

3.5.2 Palliative

- Carboplatin AUC5 + Etoposide 100 mg/m^2 iv day 1 200mg/m^2 orally days 2 and 3 every 21 days for up to 6 cycles

4.0 VAGINA

4.1 Radical Treatment for Vaginal Cancer

Patients with disease of the upper 1/3rd of the vagina will be referred to an oncologist for consideration of radical chemoradiotherapy.

- Consider radical radiotherapy using concurrent Cisplatin 40mg/m^2 maximum 80mg every week for 5 weeks
- Consider radical radiotherapy alone if patient unsuitable for chemotherapy

Patients with disease of the lower 2/3rds of the vagina who are not considered suitable for radical surgery will be referred to an oncologist for consideration of radical chemoradiotherapy.

- Consider Cisplatin 40mg/m^2 maximum 80mg every week for 5 weeks
- Consider radical radiotherapy alone if patient unsuitable for chemotherapy

4.2 Palliative Treatment

4.2.1 Disease Limited to the Pelvis but Not Suitable for Radical Treatment

- Consider palliative radiotherapy

4.2.2 Disease Outside the Pelvis

- Consider palliative chemotherapy
- Patients with persisting focal symptoms will also be considered for palliative radiotherapy

4.2.2.1 Chemotherapy

A)	**First line**
	• Carboplatin AUC5 (AUC6 if based on Cockcroft Gault formula) and Paclitaxel 175mg/m^2 every 3 weeks for 6 cycles if suitable for combination chemotherapy NB: Carboplatin may be dosed at AUC5 based on Cockcroft Gault formula at clinician's discretion.
B)	**Second line (the following may be considered)**
	• Cisplatin 60mg/m2 day 1 and 5-Fluorouracil 300mg/m2/day days 1-21 repeated every 21 days x 6 cycles • Consider MCF if patient Mitomycin C naive.

5.0 VULVA

5.1 Radical Treatment for Vulval Cancer

Patients with potentially curable disease confined to the vulva and inguinal lymph nodes that are not considered suitable for radical surgery will be referred to an oncologist for consideration of radical chemoradiotherapy or radiotherapy alone.

- Consider Cisplatin 40mg/m^2 maximum 80mg every week for 5 weeks
- Consider radical or palliative radiotherapy alone if patient unsuitable for chemotherapy

Patients who are not considered suitable for radical treatment will be treated using a similar approach to that defined for cervical cancer.

5.2 Adjuvant

Patients who have undergone radical surgery who have risk factors for recurrence will be considered for adjuvant pelvic radiotherapy with or without chemotherapy to the sites at risk for loco-regional recurrence.

- Consider Cisplatin 40mg/m^2 maximum 80mg every week for 5 weeks
- Consider radical radiotherapy alone if patient unsuitable for chemotherapy

5.3 Palliative

5.3.1 Chemotherapy

A)	**First line**
	• Carboplatin AUC5 (AUC6 if based on Cockcroft Gault formula) and Paclitaxel 175mg/m^2 every 3 weeks for 6 cycles if suitable for combination chemotherapy NB: Carboplatin may be dosed at AUC5 based on Cockcroft Gault formula at clinician's discretion.
B)	**Second line (the following may be considered)**
	• Cisplatin 60mg/mg^2 + 5-Fluorouracil 300mg/m^2/day days 1-21 repeated every 21 days x 6 cycles

6.0 UTERUS

6.1 Epithelial Tumours (Including Carcinosarcomas)

6.1.1 Unsuitable for surgery

- Consider radical radiotherapy

6.1.2 Adjuvant

Patients who have undergone radical surgery who have high risk factors for recurrence will be considered for:

- Adjuvant pelvic radiotherapy using either external beam alone, brachytherapy alone or a combination of the two
- Adjuvant chemotherapy will be considered for patients with stage III disease and selected patients with earlier stage II adverse histological subtype
    - Carboplatin AUC5 (AUC6 if based on Cockcroft Gault formula) and Paclitaxel 175mg/m^2 every 3 weeks for 4 cycles if suitable for combination chemotherapy

NB: Carboplatin may be dosed at AUC5 based on Cockcroft Gault formula at clinician's discretion.

6.1.3 Palliative

- In ER and PR positive patients, high dose progestogens e.g. medroxyprogesterone acetate (MPA) and for those patients who respond well but subsequently progress, an aromatase inhibitor can be considered as a 2nd line treatment
- Palliative radiotherapy
- Consider chemotherapy in fit patients who are ER / PR negative and those who fail hormone manipulation
    - Carboplatin AUC5 (AUC6 if based on Cockcroft Gault formula) and Paclitaxel 175mg/m^2 every 21 days x 6 cycles

NB: Carboplatin may be dosed at AUC5 based on Cockcroft Gault formula at clinician's discretion.

- Carboplatin AUC 5 and Doxorubicin 50mg/m^2 every 21 days x 6 cycles
- Cisplatin 50mg/m^2 and doxorubicin 60mg/m^2 every 21 days x 6 cycles
- Doxorubicin 75mg/m^2 every 21 days x 6 cycles (if unsuitable for combination chemotherapy)
- Carboplatin AUC5 (AUC 6 if based on C+G formula) x 6 cycles
- Cisplatin 50mg/m^2 every 21 days for 6 cycles

6.2 Sarcomas

After initial appropriate radical surgery, patients will be considered for additional treatment in collaboration with the Superregional sarcoma service at the Royal Marsden Hospital.

6.2.1 Radical

In those patients with disease confined to the uterus where resection is curative, there is no role for adjuvant radiotherapy.

Patients with more advanced localised disease will be considered for radiotherapy on an individual basis.

6.2.2 Adjuvant

There is no standard role for adjuvant chemotherapy.

6.2.3 Palliative

Chemotherapy is to be discussed on an individual patient basis with the Royal Marsden Hospital. The following may be considered:

A)	**First line**
	• Doxorubicin 75 mg/m^2 every 21 days for 6 cycles
B)	**Second line**
	• Gemcitabine 900 mg/m2 days 1 and 8 + Docetaxel 100mg/m2 day 8 every 21 days for 6 cycles for use where no previous radiotherapy has been given (funding approval required) • Gemcitabine 675 mg/m2 days 1 and 8 + Docetaxel 75mg/m2 day 8 every 21 days for 6 cycles for use where previous radiotherapy has been given (funding approval required)

7.0 APPENDIX A: DOSE MODIFICATION GUIDELINES

N.B. This section is currently under review. The information it contains is still valid but further regimens are to be added in the next version.

The following are intended to provide general guidance in the management of chemotherapy-related toxicity, but individual patients should be discussed with the treating oncologist.

7.1 Haematological Toxicity

This section provides general guidelines on the management of haematological toxicity. Please also see individual drug regimens (section 7.2) for regimen-specific considerations.

First Line Therapy

For first line chemotherapy treatment, there is some evidence that maintenance of dose intensity may be important in determining outcome. Therefore, it is advised to use prophylactic G-CSF in place of dose reduction or delay for patients experiencing neutropenia.

Treatment should proceed if on the day of chemotherapy ANC $\geq 1.0 \times 10^9$/l and platelets ≥ 75. Consider prophylactic G-CSF if treatment proceeds with a neutrophil count between 1.0 and 1.5.

If the ANC or platelets are below these parameters, treatment should be delayed until they are met. G-CSF should be given with subsequent cycles if a treatment delay is required due to neutropenia.

A 25% dose reduction should be applied in the event of neutropenia complicated by infection or prolonged (>5 day) neutrophil count < 0.5 despite the use of G-CSF.

A 25% dose reduction should also be applied in the event of severe thrombocytopenia (nadir platelets <10 or platelet count failure to recover to >75 after 1 week delay).

A further 25% dose reduction is required for a second occurrence of these toxicities. If there is a third occurrence, treatment should be discontinued.

Second and subsequent line therapy

Evidence is lacking for an impact of dose intensity, therefore in most situations dose reduction or delay should be considered for haematological toxicity, but prophylactic G-CSF may be used at the discretion of the consultant oncologist for patients experiencing neutropenia as a complication of treatment.

Treatment should proceed if on the day of chemotherapy ANC $\geq 1.5 \times 10^9$/l and platelets ≥ 100.

If the ANC or platelets are below these parameters, treatment should be delayed until they are met.

A 25% dose reduction should be applied in the event of neutropenia complicated by infection or prolonged (>5 day) neutrophil count < 0.5.

A 25% dose reduction should also be applied in the event of severe thrombocytopenia (nadir platelets <25 or platelet count failure to recover to >75 after 1-week delay).
A further 25% dose reduction is required for a second occurrence of these toxicities. If there is a third occurrence, treatment should be discontinued.

7.2 Regimen-Specific Dose Modification Guidelines

1. Carboplatin AUC5 (AUC6 if based on Cockcroft Gault formula) and Paclitaxel 175mg/m^2 every 21 days x 6 cycles

NB: Carboplatin may be dosed at AUC5 based on Cockcroft Gault formula at clinician's discretion.

Carboplatin dose is calculated according to the Calvert formula using the EDTA-estimated GFR wherever possible, when the dose in mg equals 5 x (GFR + 25).
If chemotherapy needs to be commenced urgently, the creatinine clearance can be calculated using the Cockcroft Gault formula, when the dose in mg equals 6 x (GFR + 25).

Haematological Toxicity

See section 7.1

Thrombocytopenia is more commonly associated with carboplatin than paclitaxel, therefore in the event of isolated thrombocytopenia, consider dose reduction of carboplatin only.

Non-Haematological Toxicity

(a) Neuropathy
Patients developing grade 2 or worse neuropathy require a 20% reduction in Paclitaxel dose and consider delay until recovery to grade 1 or less. In the event of recurrent grade 3 or worse neurotoxicity, or recurrent or persistent grade 2 or worse neuropathy following a dose reduction, consideration should be given to omitting Paclitaxel treatment.

(b) Hypersensitivity reactions
Patients developing hypersensitivity reactions to Paclitaxel may be re-challenged with full dose Paclitaxel following prophylactic medication e.g.:

- Hydrocortisone 100mg IV pre-med 30 minutes prior to receiving Paclitaxel, then give Paclitaxel over 3-6 hours (i.e. starting at over 6 hours and gradually increase rate if possible)
- Ranitidine 50 mg IV 30 minutes prior to receiving Paclitaxel,
- Chlorphenamine 10 mg IV 30 minutes prior to receiving Paclitaxel.

(c) Renal function
Renal function should be monitored. Discuss with consultant if creatinine clearance drops by 25%.

(d) Other grade 3 or 4 non-haematological toxicity should be managed by delaying further treatment until recovery to grade 1 or less and subsequent dose reduction by 25-100% dependent on assessment of causality.

2. Carboplatin AUC 5 IV every 3 weeks

Haematological Toxicity
See section 7.1

Non-Haematological Toxicity
No dose modification is required for non-haematological toxicity.

Renal function should be monitored. Discuss with consultant if creatinine clearance drops by 25%.

3. Caelyx 40-50 mg/m^2 IV every 4 weeks

Treatment of ovarian cancer patients who are receiving Caelyx as third or subsequent-line therapy with the licensed dose of 50 mg/m^2 IV every 4 weeks has resulted in high rates of non-haematological toxicity, in particular palmar plantar erythrodysesthesia and mucositis. The incidence is substantially reduced when a lower starting dose of 40 mg/m^2 IV every 4 weeks is employed, with comparable activity reported (albeit in non-randomised studies). The lower dose is therefore recommended in this setting.

Haematological Toxicity
See section 7.1

Non-haematological Toxicity

(a) Palmar plantar erythrodysesthesia

Grade	Symptoms	1st occurrence	2nd occurrence	3rd occurrence
1	Mild erythema swelling or desquamation not interfering with daily activities	Continue at full dose	Continue at full dose	Consider 25% dose reduction
2	Erythema, desquamation or swelling interfering with but not precluding normal activities; can wear regular cloth	Delay until recovery. Retreat at full dose	Delay until recovery. Reduce dose by 25%.	Delay until recovery. Reduce dose by 50%
3	Blisters, ulceration or swelling interfering with walking or normal activities; cannot wear regular cloth	Delay until recovery. Reduce dose by 25%.	Delay until recovery. Reduce dose by 50%.	Discontinue
4	Diffuse or local process causing infectious complications, or a bed-ridden state or hospitalization	Delay until recovery. Reduce dose by 50%.	Discontinue	

(b) Oral mucositis

Grade	Symptoms	1st occurrence	2nd occurrence	3rd occurrence
1	Painless ulcers, erythema or mild soreness	Continue at full dose	Continue at full dose	Consider 25% dose reduction
2	Painful erythema, oedema or ulcers but can eat	Delay until recovery. Retreat at full dose	Delay until recovery. Reduce dose by 25%.	Delay until recovery. Reduce dose by 50%
3	Painful erythema, oedema or ulcers and cannot eat	Delay until recovery. Reduce dose by 25%.	Delay until recovery. Reduce dose by 50%.	Discontinue
4	Requires parenteral or enteral support	Delay until recovery. Reduce dose by 50%.	Discontinue	

(c) In the event of any other grade 3 or 4 toxicity, dose reduction by 25-100% should be considered, depending on assessment of causality.

4. Paclitaxel 175 mg/m^2 IV every 3 weeks

Haematological Toxicity
See section 7.1

Non-haematological Toxicity

(a) Neuropathy
Patients developing grade 2 or worse neuropathy require a 20% reduction in Paclitaxel dose and consider delay until recovery to grade 1 or less. In the event of recurrent grade 3 or worse neurotoxicity, or recurrent or persistent grade 2 or worse neuropathy following a dose reduction, discontinue Paclitaxel treatment.

(b) Hypersensitivity reactions
Patients developing hypersensitivity reactions to Paclitaxel may be re-challenged with full dose Paclitaxel following prophylactic medication e.g.:

- Hydrocortisone 100mg IV pre-med 30 minutes prior to receiving Paclitaxel, then give Paclitaxel over 3-6 hours (i.e. starting at over 6 hours and gradually increase rate if possible)
- Ranitidine 50 mg IV 30 minutes prior to receiving Paclitaxel,
- Chlorphenamine 10 mg IV 30 minutes prior to receiving Paclitaxel.

(c) Other grade 3 or 4 non-haematological toxicity should be managed by delaying further treatment until recovery to grade 1 or less and subsequent dose reduction by 25-100% dependent on assessment of causality.

5. Paclitaxel 80 mg/m^2 IV weekly

Haematological Toxicity
See section 7.1
At consultant's discretion, weekly treatment may proceed if ANC>1.0 and platelets>75

Non-haematological Toxicity

(a) Neuropathy
Patients developing grade 2 or worse neuropathy require a 20% reduction in Paclitaxel dose and consider delay until recovery to grade 1 or less. In the event of recurrent grade 3 or worse neurotoxicity, or recurrent or persistent grade 2 or worse neuropathy following a dose reduction, discontinue Paclitaxel treatment.

(b) Hypersensitivity reactions
Patients developing hypersensitivity reactions to Paclitaxel may be re-challenged with full dose Paclitaxel following prophylactic medication e.g.:

- Hydrocortisone 100mg IV pre-med 30 minutes prior to receiving Paclitaxel, then give Paclitaxel over 3-6 hours (i.e. starting at over 6 hours and gradually increase rate if possible)
- Ranitidine 50 mg IV 30 minutes prior to receiving Paclitaxel
- Chlorphenamine 10 mg IV 30 minutes prior to receiving Paclitaxel.

(c) Other grade 3 or 4 non-haematological toxicity should be managed by delaying further treatment until recovery to grade 1 or less and subsequent dose reduction by 25-100% dependent on assessment of causality.

6. Paclitaxel 80 mg/m^2 IV weekly + Carboplatin AUC 5 every 3 weeks

Haematological Toxicity
See section 7.1
At consultant's discretion, weekly treatment may proceed if ANC>1.0 and platelets>75
In case of isolated thrombocytopenia, consider dose reduction in carboplatin alone.

Non-haematological Toxicity

(a) Neuropathy
Patients developing grade 2 or worse neuropathy require a 20% reduction in Paclitaxel dose and consider delay until recovery to grade 1 or less. In the event of recurrent grade 3 or worse neurotoxicity or recurrent or persistent grade 2 or worse neuropathy following a dose reduction, consideration should be given to omitting Paclitaxel treatment.

(b) Hypersensitivity reactions
Patients developing hypersensitivity reactions to Paclitaxel may be re-challenged with full dose Paclitaxel following prophylactic medication e.g.:

- Hydrocortisone 100mg IV pre-med 30 minutes prior to receiving Paclitaxel, then give Paclitaxel over 3-6 hours (i.e. starting at over 6 hours and gradually increase rate if possible)
- Ranitidine 50 mg IV 30 minutes prior to receiving Paclitaxel,
- Chlorphenamine 10 mg IV 30 minutes prior to receiving Paclitaxel.

Patients developing hypersensitivity reactions to Carboplatin may be considered for Carboplatin desensitisation.

(c) Other grade 3 or 4 non-haematological toxicity should be managed by delaying further treatment until recovery to grade 1 or less and subsequent dose reduction by 25-100% dependent on assessment of causality.

7. Carboplatin AUC 2.5 weekly

Haematological Toxicity
See section 7.1
At consultant's discretion, weekly treatment may proceed if ANC>1.0 and platelets>75

Non-haematological Toxicity

No dose modification is required for non-haematological toxicity.
Renal function should be monitored. Discuss with consultant if creatinine clearance drops by 25%.

Patients developing hypersensitivity reactions to Carboplatin may be considered for Carboplatin desensitisation.

8. BEP

Haematological Toxicity
See section 7.1
Day 8 and 15 treatment should proceed if ANC>0.5 and platelets>75

Non-haematological Toxicity
Pulmonary toxicity related to Bleomycin is unpredictable. Patients should have a CXR performed prior to each cycle of BEP and bleomycin should be omitted if any evidence of pneumonitis develops.

Bleomycin should be omitted from the 4th cycle.

Dose modification for non-haematological toxicity should be avoided as far as possible, but in the event of grade 3 or 4 toxicity, treatment should be delayed until resolution to grade ≤ 1 and appropriate supportive therapy instituted.

9. Gemcitabine

Haematological Toxicity

See section 7.1

In regimens incorporating gemcitabine on day 1 and 8 of a 3-weekly schedule, day 8 treatment may be administered at 75% dose if neutrophils 1.0-1.49 and/or platelets 75-99

Non-haematological Toxicity

Dose modification is rarely required for non-haematological toxicity. In the event of grade 3 or 4 non-haematological toxicity further treatment should be delayed until recovery to grade 1 or less and subsequent dose reduced by 25-100% dependent on assessment of causality.

10. Bevacizumab

Haematological Toxicity

No dose delays or dose reductions are required for haematological toxicity

Non-haematological Toxicity

See Network Chemotherapy Prescribing documents: Guidelines for Bevacizumab induced hypertension: Kent and Medway Cancer Collaborative - Network Chemotherapy Prescribing documents

9.0 APPENDIX B: CLINICAL TRIALS

Refer to the local research team who will provide on request an orientation handbook, list of current trials and associated trial protocols and summaries.

Contact numbers

MTW – Clinical Trials Office	01622 225 033
Darent Valley Hospital – Clinical Trials Office	01322 428 100 ext. 4810
Medway Hospital – Clinical Trials Office	01634 825 094

East Kent Hospitals – Clinical Trials Office:

Solid Tumours (excluding Gynae)	01227 866 393
Gynae Clinical Trials	01843 234 343
Haematology Clinical Trials	01227 864 129

10.0 PERSONNEL AND CONTACT INFORMATION

A comprehensive, up to date list of MDM contact details can be requested by NHS professionals by contacting the Kent & Medway Cancer Collaborative. Their contact telephone number is 01233 651905.

11.0 GLOSSARY

Acronyms in common usage throughout KMCC documentation

BNF	British National Formulary
BOPA	British Oncology Pharmacist Association
CNB	Cancer Network Board
COSHH	Control of substances hazardous to health regulations.
CYP	Children & Young People (in relation to the IOG)
DCCAG	Diagnostic Cross Cutting Advisory Group
DOG	Disease Orientated Group (NSSG/TSSG/TWG)
DVH	Darent Valley Hospital
DGT	Dartford and Gravesham NHS Trust
EK	East Kent
EKHUFT	East Kent Hospitals University Foundation Trust
EPS	Electronic Prescribing System
FP10(HNC)	Prescriptions issued by hospital doctors for dispensing in the community
GP	General Practitioner
HoP	High Level Operational Policy
IOSC	Improving Outcomes: A Strategy for Cancer
IV	Intravenous
K&C	Kent & Canterbury Hospital, Canterbury, (EKHUFT)
KMCC	Kent & Medway Cancer Collaborative
KMCRN	Kent & Medway Cancer Research Network

KOMS	Kent Oncology Management System
LSESN	London & South East Sarcoma Network
MFT	Medway Foundation Trust
MTW	Maidstone & Tunbridge Wells NHS Trust
NHS	National Health Service
NMP	Non-medical prescriber
NPSA	National Patient Safety agency
NOG	Non-Surgical Oncology Group *(Permanent oncologist sub group of the DOGs with a specific responsibility for chemo/rad pathways and advice to the DOG, Network and GEOGRAPHICAL LOCATIONs on new drugs)*
PoC	Pathway of Care *(Network agreed disease site specific clinical guidelines)*
QEQM	Queen Elizabeth the Queen Mother Hospital, Margate (EKHUFT)
QoL	Quality of life
QSIS	Quality service information system
QST	Quality Surveillance Team
RAT	Research and Trial Group *(Permanent sub-group of the DOGs with a specific responsibility for taking forward the clinical trials agenda)*
RMH	Royal Marsden Hospital
RNOH	Royal National Orthopaedic Hospital
SACT	Systemic Anti-Cancer therapy
SACT regimen	Systemic Anti-cancer prescription on the electronic prescribing system
SACT protocol	Systemic Anti-cancer protocol on KMCC website
TTO	Treatment to take home
QVH	Queen Victoria Foundation Trust Hospital East Grinstead
UCLH	University College Hospital London
WHH	William Harvey Hospital, Ashford (EKHUFT)
WK	West Kent

12.0 DOCUMENT ADMINISTRATION

Document Title	Oncological Treatment Guidelines for Gynae Cancer
Principle author	Gynae NOG
Co-author(s)	Gynae NOG
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Revision History			
Date of revision	New Version Number	Nature of Revision	Confirmation of Accuracy by
Feb 2006	V1	The Management of Gynaecological Cancer "Oncological Provision"	Gynae DOG
March 2009	V0.1 – 0.6 (new format)	Numerous changes to original document	Gynae NOG
March 2009	V1	Minor changes to Introduction and section 6.2.3	Gynae NOG
March 2009	V2		Gynae NOG
July 2009	V2.1	Additions to the document following discussion at Gynae NOG	Gynae NOG
September 2009	V3	Changes and additions following discussion at NOG	Gynae NOG
September 2009	V3.1	Updated to reflect FAD from NICE on topotecan and cisplatin for cervical cancer	Gynae NOG
October 2009	V4		
June - November 2010	V4.1-4.2	Updated to include the revised version of the carboplatin desensitising protocol and other minor changes from the NOG.	
November 2010	V5	Changes published	
April 2011	V5.1	Updated to include dose modification guidelines for Carboplatin AUC 2.5 weekly as single agent and in combination with Paclitaxel	
May 2011	V6	Published	
March- July 2012	V6.1-6.2	Updated to include: • bevacizumab • topotecan weekly x3 out of 4 weeks • inclusion of myocet as an alternative treatment for ovarian cancer whilst caelyx is unavailable • revision of dose modification guidelines	
March 2013	v7	Published (with revision of dose modification guidelines on-going)	
April 2013	v7.1-7.2	Updated in line with NCDF and NHSE lists	
June 2013	V8	Published	
Dec 13 – Mar 14	V8.1	Changes agreed at Gynae NOG Updated in line with NCDF list.	
April 2014	v9	Published	
June 2016 onwards	9.1-9.3	Updated in line with NICE TA 389 for funding arrangements Review of management of paclitaxel hypersensitivity and dose reductions for	

		neuropathy. Change to monitoring parameters for renal function in carboplatin containing regimens – both amended in dose modification guidelines.	
June 2017	10	Published	Gynae NOG 06/03/2018 and 17/07/18
March 2018	v10.1 – 10.3	Draft Inclusion: 2.1.2.2 Letrozole after first line chemotherapy Inclusion: 3.2 Neo- Adjuvant Treatment 2.1.2.4 section d) updated	Gynae NOG
August 2018	V11	Published	Gynae NOG
December 2019	V11.1	Draft Addition of section 2.1.2.2 Maintenance treatment following first line chemotherapy Amendment to section 2.1.2.5 Second and subsequent line chemotherapy	Gynae NOG
September 2020	V11.2	Amendments to sections 1.0, 2.1.2.5, 2.2, removal of appendix B	Gynae NOG 02.03.21
March 2021	V11.3 – 11.4	2.1.2.2 addition of niraparib 2.1.2.6 addition of Overview of PARP inhibitors for ovarian cancer table Acronym table updated. Reformatted by R Patel	Gynae NOG Updated virtually
	V11.5	Addition of Olap and Bev to PARP inhibitor table and 2nd line Olap maintenance	
July 2021	V12	Published	Approved by Gynae NOG