Pan Birmingham NHS
Cancer Network

Guidelines for the Management of Patients with Gynaecological Cancers with Chemotherapy

Version History

Version	Date	Summary of Change/Process
1.0	24.11.08	Approved by the Governance Committee Chair
1.1	09.09.11	Reviewed and updated by Sarah Williams
1.2	11.10.11	Circulated for reviewing to Gynae Network Site Specific Group and Oncologists
1.3	03.11.11	Reformatted by Lara Barnish, with comments from Indy Fernando and Ahmad El-Modir
1.4	08.11.11	With addition re sarcoma from Karen Metcalf
1.5	16.11.11	With comments from Sarah Williams
1.6	21.11.11	With comments from Alison Rowe
1.7	21.11.11	Prepared for reviewing by Suhail Anwar
1.8	30.11.11	Reviewed and updated by Suhail Anwar
2.0	30.1111	Reviewed and endorsed by Network Guidelines Sub Group

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Changes Between Version 1 and 2

Section 3

- Neoadjuvant chemotherapy is no longer reserved for inoperable disease but is now considered as first line treatment option for stage 3C/4 disease.
- Current guidelines recommend all patients receiving neoadjuvant chemotherapy are considered for surgery after 3 cycles of chemotherapy.
- Updated recommendations on carboplatin dosing.

Section 4

- Carboplatin and liposomal doxorubicin added as a treatment choice for patients with platinum sensitive relapsed disease.
- Rotterdam regimen/letrozole added as options for the management of platinum resistant disease.

Section 5

- Carcinosarcomas added as a separate section.

Section 6

- Reference to sarcoma Multi Disciplinary Team (MDT) and guidelines added.
- Trabectedin added as a treatment.
- Endometrial stromal sarcomas added as a separate section.

1. Scope

This guidance has been produced to support the management with chemotherapy of patients who have gynaecological cancers.

2. Guideline background

2.1 All patients are formally reviewed by a Specialist Multi Disciplinary Team (SMDT). Chemotherapy treatments are delivered under the care of SMDT members, where possible at a Trust local to the patient.

2.2 All Trusts undertaking gynaecological surgery in the Pan Birmingham Cancer Network are recognised as cancer units. One hospital (Sandwell and West Birmingham Hospitals NHS Trusts: City Hospital site) is recognised as the Gynaecological Cancer Centre.

Guideline statements

3. Epithelial ovarian cancer: first line chemotherapy (see Guideline for the assessment, management and referral of patients with suspected ovarian cancer)

3.1 International Federation of Gynaecology and Obstetrics (FIGO) stage I - 3B

3.1.1 Patients with low risk surgically staged FIGO stage IA and IB grade1\grade 2 adenocarcinomas would not be recommended adjuvant chemotherapy.

3.1.2 Patients with surgically staged FIGO IA and IB disease with high risk histology such as grade 3 serous or clear cell tumours and all stage 2 and 3 patients who have undergone debulking surgery should be offered adjuvant chemotherapy:

a) patients should be offered platinum based adjuvant chemotherapy of carboplatin* AUC 6 +/- paclitaxel 175mg/m^2 every 3 weeks for 6 cycles.
b) for patients with stage I disease consideration to the use of single agent carboplatin* AUC 6.0 for 6 cycles may be given as per NICE guidance of April 2011
c) for stages 2 and 3 the regimen of choice would be 3 weekly carboplatin* AUC 6.0* and paclitaxel 175mg/m2 unless the patient has a medical contraindication to paclitaxel or declines the additional toxicity associated with this.

3.1.3 Adjuvant chemotherapy should commence within 6 weeks of radical debulking surgery.

3.2 FIGO stage 3C and 4V

3.2.1 Primary debulking surgery remains a standard for all patients assessed to have resectable advanced ovarian cancer. All patients with stage 3 and 4 disease should be evaluated for their suitability for primary debulking surgery.

3.2.2 Following the results of the EORTC randomised study published by Vergote et al.[7] and a wealth of published retrospective case series, neoadjuvant chemotherapy represents a valid alternative treatment choice for patients with advanced disease and should be offered to the following patients:

a) those with unresectable disease.
b) patients in whom optimal debulking is not deemed possible on clinical or radiological assessments.
c) where it is considered that delayed surgery would offer the patient a benefit in terms of treatment associated morbidity.

3.2.3 The decision to proceed with primary debulking surgery versus neoadjuvant chemotherapy should be made on an individual case basis after discussion at the relevant multi disciplinary team (MDT) and discussion with the patient.

a) adjuvant chemotherapy:

Following an attempt at radical debulking surgery patients should be offered adjuvant chemotherapy with carboplatin* AUC 6 - 7.5 and +/- paclitaxel 175mg/m^2 every 3 weeks for a minimum of 6 cycles, or a maximum of 8 cycles.

b) neoadjuvant chemotherapy:

Neoadjuvant chemotherapy with carboplatin* AUC 6.0 +/- paclitaxel 175mg/m2* should be offered every 3 weeks for 3 cycles followed by assessment for resectability. Resectability should routinely be assessed by clinical review (by a gynaecological oncologist) and radiological assessment followed by MDT discussion.

i. patients considered suitable for delayed debulking surgery should be offered surgery within 4 weeks of day 1 of cycle 3 provided they have adequately recovered from chemotherapy. Following surgery and in the absence of mitigating complications chemotherapy will resume within 4 weeks and the patient will complete 6 - 8 cycles of chemotherapy in total. The priority must be to minimise treatment gaps between therapies. Where delays are unavoidable for clinical reasons, surgery after cycle 4 or 5 may be necessary but arrangements should be individualised to ensure adequate adjuvant therapy is given following surgery.

ii. patients considered unsuitable for surgery after 3 cycles of chemotherapy but demonstrating evidence of response should continue with chemotherapy to 6 cycles and be rediscussed for consideration of surgery after 6 cycles have been completed. In these patients if delayed surgery is performed after 6 cycles of chemotherapy, consideration to 2 further cycles of chemotherapy should be given post-operatively in the adjuvant context.

c) Single agent carboplatin *****

3.3 Patients with the following characteristics or co-morbidities should be considered for single agent carboplatin* (AUC 6) every 3 weeks for 6 cycles:

a. significant organ dysfunction, especially jaundice.
b. pre-existing neuropathy: G2 or above.
c. diabetes mellitus, with neurovascular complications.
d. medical co-morbidities that in the opinion of the clinician precludes the use of paclitaxel.
e. those unwilling to consider any risk of hair loss, or unhappy to have paclitaxel, after discussion.
f. based on clinical assessment, patients with impaired performance status, advanced age or extensive medical co-morbidities may be considered initially for reduced dose chemotherapy with carboplatin* at AUC 4 - 5. However, the dose should be reassessed if the general status of the patient improves for subsequent cycles.
g. ***patients developing neuropathy with paclitaxel can be considered for carboplatin* and docetaxel (SCOTROC protocol)***

3.3 *Notes on carboplatin dosing

3.3.1 Since carboplatin is renally cleared without prior metabolism, pharmacokinetically guided dosing based on renal function is now standard worldwide, using the Calvert formula. Renal clearance may be calculated using either Cockcroft or Wright formulae. The suggested AUC-framed doses cited in the guidelines above refer to renal clearance based on the Cockcroft Gault formula: however, if chromium-labelled EDTA GFR measurement or Wright formula is used, then doses should be reduced, typically from AUC 6 to AUC 5, since Wright and EDTA GFR reads high.

3.3.2 In patients with serum creatinine <50 strong consideration should be given to GFR measurement with chromium labelled EDTA or 24 hour urine collection due to the possibility of falsely elevated GFR calculations being achieved with the above calculated formulae.

3.3.3 Current international guidance recommends that 900mg be used as the ceiling dose for patients treated with carboplatin* at an AUC of 6.0. The

Calvert formula is only considered robust for GFR's up to 125 and thus a ceiling dose of 900mg is recommended.

4. Ovarian cancer: relapsed disease

4.1 Those with a 6 months or longer platinum free survival

4.1.1 For patients of good performance status, who relapses without evidence of ascites or disseminated disease consideration of the role of secondary debulking surgery, should be discussed at the SMDT.

4.1.2 Patients not suitable for surgery should be considered for platinum based chemotherapy comprising one of the following:

a) carboplatin* AUC 6 every three weeks for six cycles.
b) carboplatin* AUC 6 and paclitaxel 175 mg/m^2 over 3 hour infusion, every 3 weeks for 6 cycles.
c) carboplatin* AUC 4.0 and gemcitabine 1000mg/m^2, both repeated day 1 and day 8, repeated every 3 weeks for 6 cycles, or carboplatin* AUC 2.25 day 1, with gemcitabine 1000/m^2 days 1 and 8.
d) carboplatin* AUC 5.0 and liposomal doxorubicin 30mg/m2 q 4 weekly for 6 cycles.
e) liposomal doxorubicin (Caelyx)

4.1.3 The choice of which of the above regimens to use will be at the discretion of the treating clinician and will be based on such factors as performance status, medical co morbidities, persisting toxicities from first line treatment as well as the platinum free interval.

4.2 Those with less than 6 months platinum free survival

4.2.1 These patients should be offered one of the following depending on their circumstances:

a) liposomal doxorubicin (Caelyx) 40 - 50mg/m^2 every 4 weeks.
b) topotecan 1.25mg/m^2 – 1.5mg/m2 d1-5 every 3 weeks or 4 mg/m^2 weekly D1,8 and D15 q 28 days.
c) weekly low dose paclitaxel 70-90mg/m^2.
d) dose dense chemotherapy with weekly carboplatin* and paclitaxel (AUC 2.0 – 3.0 and 70 – 80mg/m2).
e) Dose intense cisplatin and etoposide: weekly induction regimen (cisplatin 50mg/m2 per week D1,8,15, and 29,36,43 and etoposide 50mg PO daily D1-15 and D29-43). Maintenance etoposide 50mg/m2 od 21 days q 28 may be used in responding patients.
f) oral etoposide 50mg po bd x 7-12 days adjusted *vs.* myelosuppression, serum albumin, renal function & bilirubin, repeated every 3 weeks.

g) hormonal treatment with tamoxifen 20mg daily or in the event of confirmed tumour ER positivity Letrozole 2.5mg daily might be considered as palliative treatment options.

4.2.2 Patients should be offered the opportunity to participate in phase I and II studies, this may require an out of Network referral, depending on the current local early phase trial activity.

5. Ovarian carcinosarcomas

5.1 Treatment principles as described above for epithelial ovarian carcinoma should be followed with primary debulking surgery and adjuvant chemotherapy for early stage disease or for advanced disease either primary surgery with adjuvant chemotherapy or neoadjuvant chemotherapy with delayed surgery with adjuvant chemotherapy.

5.2 Recommended chemotherapy regimens include carboplatin* AUC 5.0 and ifosphamide 3g/m2, carboplatin* AUC 6.0 and paclitaxel 175mg/m2 or single agent carboplatin* AUC 6.0 all given 3 weekly for 6-8 cycles.

6. Gynaecological sarcomas

6.1 All cases of gynaecological sarcomas should be referred to the central soft tissue sarcoma MDT based at University Hospitals Birmingham NHS Foundation Trust for confirmation of histopathological diagnosis, ratification of agreed treatment plans and advice regarding follow up.

6.2 Leiomyosarcomas and high grade undifferentiated gynaecological sarcomas.

6.2.1 In line with current published guidelines, adjuvant chemotherapy is not routinely recommended for patients with resected uterine leiomyosarcomas due to the lack of evidence to support a survival benefit with this approach.

6.2.2 Patients with advanced stage disease or metastatic disease requiring first line treatment should be offered one of the following:

a) single agent doxorubicin 60 - 75mg/m^2 every 3 weeks for a maximum of 6 cycles, with attention to cardiac risk factors, cumulative cardiac toxicity and liver function.
b) doxorubicin 50 - 60mg/m^2 plus ifosfamide 5 - 6g/m^2 (may be given as 2.5mg/m^2 day 1 and 2) with mesna every 3 weeks for a maximum of 6 cycles).

6.3 Patients requiring second line treatment, with good performance status should be considered for:

a) Docetaxel and gemcitabine. This regimen may be delivered as a 3 weekly treatment gemcitabine 900mg D1 and 8 and docetaxel 100mg D8 with GCSF D9-15. Alternatively a two weekly regimen of docetaxel 50mg/m^2 or 60mg/m^2 day 1 and gemcitabine 1250 - 1500mg/m^2 day 1 both repeated every 14 days for 10-12 fortnightly cycles (-choice of dose depending on the marrow reserve and performance status of the patient).
b) Trabectedin 1.5mg/m2 every 3 weeks for up to 6 cycles depending on toxicity and response. Administration via a central line is strongly recommended.

6.4 Hormonal manipulation with either an aromatase inhibitor or progestogen may be considered in patients with indolent tumours in whom oestrogen and progesterone receptor positivity has been confirmed.

6.5 Endometrial stromal sarcoma:

6.5.1 In line with current published guidelines systemic adjuvant therapy is not routinely recommended although due to the hormonal responsiveness of the majority of these tumours and a small trial showing benefit consideration may be given to adjuvant progestogens in high risk patients.

6.5.2 For patients with advanced and metastatic disease hormonal manipulation with progestogen or an aromatase inhibitors is recommended.

7. Cervical cancer

7.1 See Network Guidelines for the Management of Cervical Cancer.

7.2 Treatments for patients presenting with chemo-naive (platinum unexposed) advanced disease include:

a) cisplatin 50mg/m2 and topotecan 0.75mg/m2 D1,2,3 repeated 3 weekly.
b) cisplatin 75 mg/m2 D1 + 5- fluorouracil 1000mg D1,2,3,4 repeated 3 weekly
c) cisplatin 50mg/m2 and paclitaxel 135mg/m2 repeated 3 weekly.
d) cisplatin 50mg/m2 and gemcitabine 1000mg/m2 D1 and 8 repeated 3 weekly.
e) cisplatin single agent 50 -75mg/m2.

7.3 For patients previously exposed to platinum based chemoradiation may be considered for a further platinum based regimen provided they have a durable progression free interval and maintained performance status/renal function.

7.4 In patients with poor PS or renal impairment, low dose weekly carboplatin* and paclitaxel may be considered.

8. Endometrial cancer

8.1 See Network Guidelines for the Management of Endometrial Cancer.

8.2 Patients requiring first line chemotherapy (either those with newly diagnosed advanced disease, or as adjuvant ***treatment*** for those with higher risk surgically treated stage ***3 and 4a*** disease) should be considered for the following assuming no contra-indications – see above section 3.

a. carboplatin* AUC 5.0 and doxorubicin 30mg/m2 3 weekly.
b. carboplatin* AUC 5.0 and epirubicin 50mg/m2 q 3 weekly.
c. carboplatin* AUC 6.0 and paclitaxel 175mg/m2.
d. single agent carboplatin* AUC 6.0.

8.3 Patients with resected papillary serous carcinoma of the uterus should be considered for 6 cycles of adjuvant chemotherapy with carboplatin* AUC 6.0 +/- paclitaxel 175mg/m2.

8.4 Patients with unresectable advanced disease should be offered 6 cycles of palliative chemotherapy with carboplatin* and paclitaxel. Consideration to delayed surgery may be given on an individual case basis by the MDT in patients with a good response to chemotherapy and no visceral or pulmonary metastases.

8.5 Patients with uterine carcinosarcomas can be considered for adjuvant chemotherapy with carboplatin* and ifosfamide or carboplatin* and paclitaxel or carboplatin* alone.

8.7 Patients requiring chemotherapy as second line treatment at relapse may be offered weekly paclitaxel, liposomal doxorubicin (if anthracyclines not used first line).

8.8 Progestogens and aromatase inhibitors have shown activity in ER and PGR positive tumours and may also be considered ***in stage 3 and 4 disease***.

9. Carboplatin*- related acute hypersensitivity reactions

9.1 These have been increasingly encountered in recent years, as the benefits, rationale and rules of carboplatin* re-treatment have become more widely appreciated. Their manifestations are sometimes atypical (chest pain etc) and pruritus. It is now recognised that in patients with mild to moderate reactions successful delivery of carboplatin* can be achieved using a hyposensitisation schedule. Switching to cisplatin is an option, however caution should be applied due to the risk of cross-sensitivity.

9.2 The following hyposensitisation approach is an option in patients whose initial reaction was not so serious as to compromise vital signs (systolic BP <100mmHg) and whose tumours are manifestly responding to platinum-based chemotherapy:

a) dexamethasone 20mg iv 1 hour before rechallenge.
b) chlorpheniramine 10mg and ranitidine 50mg iv 10 minutes before rechallenge.
c) carboplatin* 1mg in 500mls 5% dextrose/1 hour infusion.
d) carboplatin* 10mg in 500mls 5% dextrose/1 hour infusion.
e) carboplatin* 50mg in 500mls 5% dextrose/1 hour infusion.
f) carboplatin* [total required dose – 61mg] in 1000mls 5% dextrose/ 3 hour infusion.

9.3 Patients' vital signs should be monitored every 5 minutes x 3, during each bag. Adrenaline (1ml 1:1000 for IM injection) should be drawn up and kept to hand for use in event of anaphylaxis – please refer to Network Guidelines for Anaphylaxis

10. Patient information and counselling

10.1 All patients, and with their consent, their partners will be given access to appropriate written information during their investigation and treatment, and on diagnosis will be given the opportunity to discuss their management with a clinical nurse specialist who is a member of the relevant MDT. The patient should have a method of access to the gynae team at all times.

10.2 Access to psychological support will be available if required. All patients should undergo a holistic needs assessment and onward referral as required.

11. Palliative care

11.1 Palliative care services will be made available to all patients as deemed appropriate by the MDT.

12. Clinical trials

12.1 Wherever possible, patients who are eligible should be offered the opportunity to participate in National Institute for Health Research portfolio clinical trials and other well designed studies.

12.2 Where a study is only open at one Trust in the Network, patients should be referred for trial entry. A list of studies available at each Trust is available from Pan Birmingham Cancer Research Network. Email: PBCRN@westmidlands.nhs.uk .

12.3 Patients who have been recruited into a clinical trial will be followed up as defined in the protocol.

Monitoring of the Guideline

Implementation of the guidance will be considered as a topic for audit by the NSSG in 2013/2014.

Guidelines

- NICE Clinical guidelines CGRADE 122
- NICE Technology Appraisal Technology appraisals TA55, TA91, TA183

References

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- Monk et al. Phase 3 Trial of Four Cisplatin-Containing Doublet Combinations in Stage IVB, Recurrent, or Persistent Cervical Carcinoma: A Gynecologic Oncology Group Study JCO (2009) 27 (28) 4649 – 4655.

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