# Principles of chemotherapy and radiotherapy

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## Abstract

The current management of all gynaecological malignancy requires complex multidisciplinary investigation and discussion, leading to multi-modality treatment. The delivery of systemic therapy or radiotherapy can have different aims depending on the type of cancer, clinical context and patient wishes. This review explores the systemic treatment options and radiotherapy that form part of the standard management of this group of tumours and looks at current research that may help shape the treatment of the future.

**Keywords** cancer; cervix; chemotherapy; endometrium; ovary; radiotherapy

## Systemic therapy

Systemic therapy refers to drug treatments that travel through the bloodstream to reach cancer cells throughout the body. These agents include chemotherapy, targeted agents and endocrine therapy. Systemic therapies can be used as a curative treatment, often as part of a multi-modality approach, or as a palliative treatment to help control the disease and symptoms for as long as possible. (The aims of treatment are shown in Box 1.)

## Chemotherapy

Malignant tumours are characterised by rapid, uncontrolled cell division. The therapeutic effects of chemotherapy are produced by interrupting cell division, leading to cell death. Some chemotherapy agents can only affect cells that are dividing and are termed cell cycle specific, others can affect cells in any phase including the rest phase termed cell cycle non-specific (Figure 1).

The commonly used chemotherapy agents in gynaecological malignancy include the following:

Carboplatin and Cisplatin are Platinum agents that form intra and inter strand DNA cross links inhibiting DNA synthesis and cell replication leading to apoptosis.

Paclitaxel is a Taxane that stabilises microtubules causing mitotic halt, leading to cell death.

Liposomal Doxorubicin is an Anthracycline that binds DNA and inhibits nucleic acid synthesis leading to cell death. The liposome microscopic vesicle in which the doxorubicin sits penetrates the abnormal tumour vasculature and once in the tissue the drug is released.

Gemcitabine is an antimetabolite that works as a nucleoside analogue replacing cytidine during DNA replication resulting in apoptosis.

The side effects of treatment are caused by the impact on the normal tissues as they divide. Side effects can be acute, occurring during treatment or late, occurring months to years later. The greatest impact of chemotherapy is seen in normal cells which have a high cell turnover such as hair follicles, mucosal lining cells of the GI tract and the bone marrow. The normal cells are usually able to repair the damage in between doses of treatment minimising the risk of long term damage. The different chemotherapy agents cause differing side effects and each individual experiences side effects to different degrees. Table 1 lists the potential side effects of chemotherapy.

Candidates for chemotherapy should be of WHO performance status 0–2 (Box 2), with adequate renal, hepatic and haematological function. Treatment delivered to individuals outside these specifications can lead to increased morbidity or mortality. The only exception is at the first diagnosis of an advanced rapidly progressing chemo-sensitive cancer when giving a usually well tolerated chemotherapy, such as carboplatin, to a poor performance status patient may allow symptomatic relief and physical improvement.

Intravenous (IV) chemotherapy is delivered in cycles. The duration of the cycle varies according to the drug combination used. Standard carboplatin and paclitaxel is delivered day 1 of a 21 day cycle. Administering treatment in this way allows the normal cells to recover prior to the next cycle and allows the cancer cells to travel through the cell cycle to a more vulnerable phase improving cell kill.

## Dose dense chemotherapy

Dose Dense Chemotherapy involves giving treatment more frequently than every 3 weeks.

Carboplatin given every 3 weeks and paclitaxel given weekly is being assessed in trials. To date studies have shown some benefits in progression free survival and overall survival, mainly in those with over 1 cm of residual disease after surgery. Those with clear cell or mucinous carcinomas or those receiving bevacizumab did not seem to benefit from dose dense treatment although further results are awaited and the toxicity of treatment has been reported as being worse in the dose dense arm. In the UK the ICON8 and ICON8b studies are looking at dose dense treatments with and without bevacizumab. ICON8b is currently still recruiting patients. Dose dense treatment is not part of UK standard practice outside trials in first line treatment at present.

## Intraperitoneal chemotherapy

Intraperitoneal chemotherapy (IP) is a subject of investigation Internationally, but is not part of UK standard practice at present and there is no consensus among ovarian cancer experts on whether IP therapy should be given as part of standard treatment for women with optimally de-bulked early ovarian cancer. Compared with intravenous treatment, intraperitoneal administration permits a significantly higher drug concentration to be achieved within the abdominal cavity. Analysis of intra-tumoral

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## Treatment aims

**Radical** – Treatment delivered without surgery with the aim of cure.
**Neo-adjuvant** – Treatment delivered before surgery to maximise the chance of a complete resection and cure.
**Adjuvant** – Treatment delivered after surgery to reduce the risk of cancer relapse and increase cure rate.
**Palliative** – Treatment delivered to control the cancer or symptoms from cancer when cure is not possible.

**Box 1**

drug concentrations demonstrates that lesions smaller than 3 mm have significantly higher drug exposure from IP administration compared with IV administration.

Studies have looked at treating women with optimally debulked disease (no residual or less than 1 cm of residual disease) who had not received neoadjuvant treatment with a combination of IV and IP chemotherapy. The most commonly used IV/IP regimen comes from GOG 172 and combines intravenous paclitaxel day 1, intraperitoneal cisplatin day 2, intraperitoneal paclitaxel day 8 repeated six times.

The main meta-analysis showed that compared to IV treatment alone, the IV/IP regimen resulted in a reduced risk of death and better disease free survival, although higher toxicity was seen. There are limitations to the meta-analysis as the IV treatment delivered differed between the studies and could have influenced outcome. There is no current data on the use of IP chemotherapy after neo-adjuvant therapy and interval debulking surgery.

IP chemotherapy is delivered through an implanted port placed at the time of surgery or at a later date. The patient is moved from side to side every 15 minutes for 1 hour to help disperse the chemotherapy. The main complications include higher neurotoxicity compared with IV treatment, nephrotoxicity, abdominal pain, peritonitis, bowel obstruction, bowel necrosis and perforation.

## Targeted therapy

Targeted drugs act on specific molecular targets involved in the growth or spread of cancer cells. As these targets are not found in high concentration in normal cells the side effects are much less when compared to chemotherapy.

These agents can be divided into two categories:

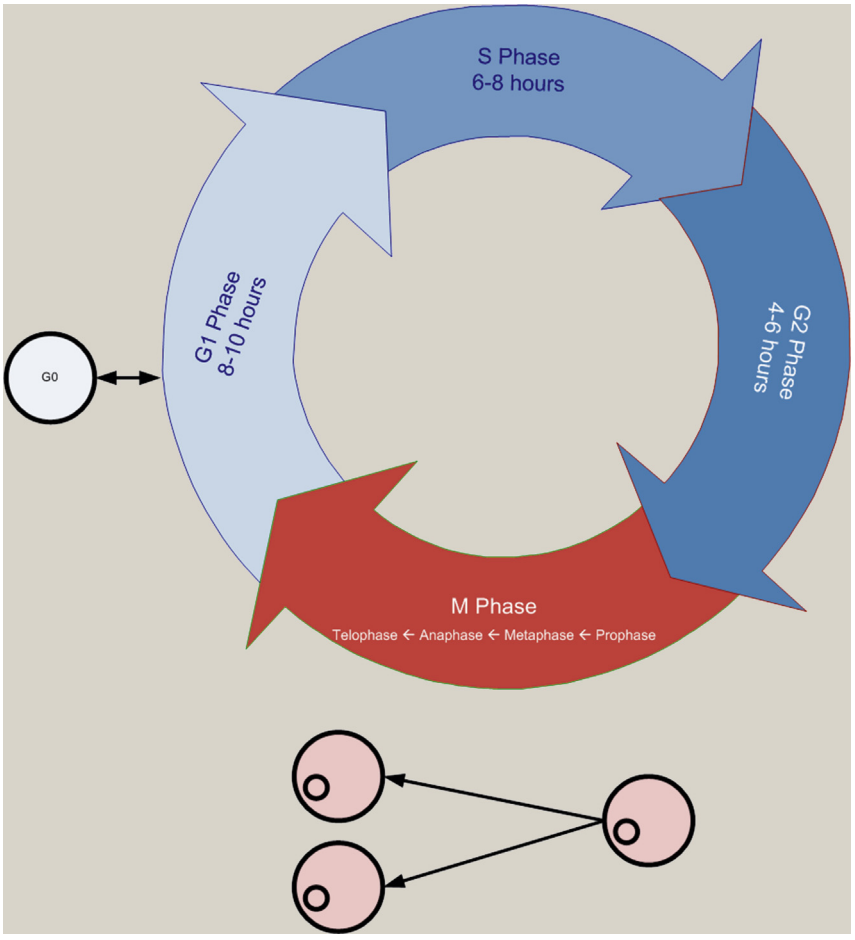


**Figure 1** The Cell Cycle. **G0: rest phase**. The cell is outside the cell cycle and not dividing. **G1 phase**: rapid growth and metabolic activity, mRNA and protein synthesis. **S phase**: growth and DNA replication. **G2 phase**: growth, protein synthesis and final preparation for division. **M phase**: Prophase – chromatin condenses into chromosomes; Metaphase – chromosomes attach to the spindle fibres; Anaphase – chromosomes move to opposite poles of the spindles; Telophase – two nuclei are formed; Cytokinesis – the cell cytoplasm splits into two forming two cells.




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