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8 Chemotherapy: principles and applications

Introduction
Chemotherapy is used in a variety of situations in gynaecological oncology. The best known is in the treatment of gestational trophoblastic disease, where single-agent treatment is highly successful for low-risk cases and multi-agent regimens are used in the treatment of higher-risk cases. Gestational trophoblastic disease is one of the few solid tumours that is regularly cured by chemotherapy alone. It is, however, an uncommon tumour. The most common use in gynaecology is in the treatment of epithelial and non-epithelial ovarian cancers.

Chemotherapy is used in an adjuvant setting (after a primary surgical procedure that may or may not have removed all macroscopic disease), in a ‘neoadjuvant’ fashion (prior to a surgical procedure) and in relapsed or recurrent disease. In cervical cancer, chemotherapy is usually reserved for selected cases of relapsed disease, although, latterly, it has been employed concurrently with radiotherapy in primary treatment (chemoradiation). This principle is also being applied to selected cases of vulval cancer, although less frequently.

In endometrial cancer, chemotherapy is used to treat advanced or relapsed cases where surgery and or radiotherapy are considered

USES OF CHEMOTHERAPY IN GYNAECOLOGICAL ONCOLOGY
- Adjuvant and neoadjuvant treatment in ovarian cancer
- Primary treatment of gestational trophoblastic disease
- Relapsed ovarian cancer
- Advanced or relapsed cervical cancer
- Chemoradiation in cervical and vulval cancer
- Advanced and relapsed endometrial cancer
- Sarcomas and non-epithelial ovarian tumours
inappropriate, although hormone treatment is also used in these situations. Finally, chemotherapy may be used as sole or part therapy for gynaecological sarcomas. It should be stressed that the evidence supporting the use of chemotherapy in advanced endometrial cancers, sarcomas and some non-epithelial tumours is weak. This is largely a result of the infrequency with which these conditions are encountered.

**Treatment intent**

In some situations, the intent of treatment may be curative, an example being trophoblastic tumours, while in others the intent is palliative, for example in recurrent epithelial ovarian cancer. It is one of the most basic principles of cancer care that this intent should be clearly understood at the outset. This is not only because clear and understandable patient information requires it but also because without understanding intent it is impossible to balance risks with benefit. Most, if not all, cytotoxic drugs have adverse effects, some of which can be severe and life threatening. These risks may be acceptable to the patient (and her carers) if the benefit is potential cure; they may not be if palliation is the primary objective (see Chapter 15).

**Toxicity**

In all of the situations above, conventional chemotherapy used to kill tumour cells will also kill normal, healthy cells. This gives rise to treatment-related toxicity such as myelosuppression, emesis, alopecia and peripheral neuropathy. A balance must be achieved between the effect upon tumour cells and the potential morbidity due to treatment-specific toxicities. Some toxic effects of chemotherapy, such as emesis, can be controlled effectively by the use of 5-HT antagonists such as ondansetron, while others, such as severe myelosuppression, can be life threatening.

Drugs with differing toxicities are often used in combination to try to maximise the cytotoxic effect upon the tumour without an associated increase in morbidity.

Many features combine to allow the selection of appropriate agents, toxicity being one important parameter. The objective is of course to choose the least toxic regimen (single agent or combined) that has known activity in the disease. The mechanism of action of various drugs differs, as do their pharmacokinetic properties. In most instances when chemotherapy fails, it is due to the development of drug resistance and thus the prevention of resistance is high on the agenda when treatment is being planned. Strategies to try to prevent the development of drug resistance include the use of non-crossreacting agents in multi-drug regimens, drugs with different toxicities, dose, route of administration and
Table 8.1 Complications of chemotherapy

<table>
<thead>
<tr>
<th>Organ/system</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological</td>
<td>Myelosuppression, common with carboplatin, can cause granulocytopenia. Granulocytopenia: predisposes to sepsis. Use prophylactic, broad-spectrum antibiotics in febrile granulocytopenic patients. Thrombocytopenia: with a risk of spontaneous haemorrhage. Anaemia: usually presents after several courses of chemotherapy.</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea and vomiting, common adverse effects. 5-HT₃ antagonists are effective treatment. Mucositis: mouth and pharyngeal ulceration. Oesophagitis, causing dysphagia, bowel ulceration resulting in diarrhoea or necrotising enterocolitis (NEC) in severe cases with granulocytopenia. Treatment is with intravenous hydration, electrolyte replacement, antimotility drugs e.g. codeine phosphate and vancomycin in NEC.</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Acute renal failure: cisplatin, in particular, causes dose-related renal tubular toxicity. Pre- and post-treatment intravenous hydration is used. Haemorrhagic cystitis: due to the irritant effect on the bladder mucosa of acrolein, the toxic metabolite of cyclophosphamide. Hydration, diuresis and mesna (sodium mercaptoethane sulfonate) help to prevent this.</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Elevation of liver enzymes may occur.</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Many cytotoxics cause some central or peripheral neurotoxicity. Cisplatin produces ototoxicity, peripheral neuropathy, and, rarely, retrobulbar neuritis and blindness. Paclitaxel associated with peripheral sensory neuropathy. Neurotoxicity increased with combination cisplatin therapy.</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Suppression of cellular and humoral immunity predispose to opportunistic infection.</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>Associated with carboplatin, paclitaxel and anaphylaxis with cisplatin.</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Usually reversible, common with paclitaxel; associated with significant psychological morbidity.</td>
</tr>
<tr>
<td>Gonadal dysfunction</td>
<td>Infertility: many cytotoxics cause infertility. Successful pregnancies have been achieved after cisplatin-based chemotherapy. Teratogenicity: all cytotoxics carry the risk of teratogenicity.</td>
</tr>
<tr>
<td>Second malignancies</td>
<td>Cisplatin is associated with the development of acute leukaemia.</td>
</tr>
</tbody>
</table>

dose scheduling to maximise the pharmacokinetic properties of the drugs. Despite these efforts, recurrence and relapse are often seen in the
treatment of solid tumours, gynaecological cancers included.

The complications of chemotherapy are described in Table 8.1.

**Epithelial ovarian cancer**

See also Chapter 10, Ovarian Cancer Standards of Care.

Almost 75% of patients with ovarian cancer have advanced disease at presentation. In this situation, surgery alone is not curative. A large meta-analysis of studies involving almost 7000 patients with ovarian cancer found that cytoreductive surgery had only a small effect on the survival of women with advanced ovarian cancer; the type of chemotherapy was found to be more important. Around 70% of patients exhibit a response to chemotherapy administered in the adjuvant situation. However, only modest improvements in survival are observed for most patients with advanced ovarian cancer, and the overall five-year survival has remained poor, at around 25%, for the last 30 years. Chemotherapy in ovarian cancer is platinum-based and, to date, the addition of newer chemotherapeutic agents has resulted in only modest increases in survival.

During the 1980s, cyclophosphamide and cisplatinum given in combination became first-line therapy. Cyclophosphamide is an alkylating agent, which acts by cross-linkage of DNA. Cisplatinum, developed in the 1960s, has a similar mode of action to the alkylating agents. The adverse effects of cisplatinum include nephrotoxicity, emesis, neurotoxicity and ototoxicity (Table 7.1).

Carboplatin is an analogue of cisplatinum. It is less nephro- and neurotoxic and causes less vomiting than cisplatinum. Following studies showing comparable activity to cisplatinum, carboplatin was used in the International Collaboration on Ovarian Neoplasms (ICON 2) trial as a single agent versus a combination of cyclophosphamide, doxorubicin and cisplatinum (CAP). There was no difference in outcome between the two groups.

Paclitaxel, one of the taxane group of drugs, was introduced as a first-line therapy in combination with carboplatin. Extracted from the bark of the Western Yew (Taxus brevifolia), it acts by stabilising cell microtubules and thus interferes with cell replication. It can cause severe hypersensitivity reactions and its adverse effects include alopecia, neutropenia, myalgia and peripheral neuropathy. The National Institute for Clinical Excellence (NICE) now recommends the combination of carboplatin and paclitaxel as first-line adjuvant therapy in epithelial ovarian cancer (see Chapter 9). The third trial by the ICON group (ICON 3) compared paclitaxel plus carboplatin with either carboplatin alone or CAP. Presented at the American Society of Clinical Oncology (ASCO) meeting in 2000, this large
trial of more than 2000 patients, showed no difference in the outcome between the two treatment arms. As a result of this trial, the advantage of paclitaxel in combination with carboplatin over a regimen of single-agent carboplatin alone has been questioned.

Current research in chemotherapy for advanced ovarian cancer focuses on:

- development of new drugs and combinations of drugs: the combination of carboplatin and paclitaxel with drugs such as gemcitabine, docetaxel and topotecan to form ‘triplet’ chemotherapy regimens
- neoadjuvant chemotherapy: conventional chemotherapy given in three to four cycles prior to surgical debulking of advanced ovarian cancer, followed by three or four further cycles
- intraperitoneal chemotherapy: conventional drugs administered into the peritoneal cavity following surgery via peritoneal catheters
- gene therapy: novel therapeutic agents developed against tumour vasculature or targeting tumour cells directly are undergoing clinical trials at present.

**EARLY-STAGE OVARIAN CANCER**

In contrast to advanced disease, the benefit of adjuvant chemotherapy has been debated in early stage disease. Five-year survival rates of over 90% can be achieved in stage 1 disease. Presented at the European Cancer Conference in October 2001, the ICON 1 and Adjuvant Clinical Trial In Ovarian Neoplasm (ACTION) studies helped to clarify the situation. For stage 1 tumours with certain high-risk features such as clear cell histology, there is a clear survival advantage in those patients who received adjuvant chemotherapy.

**RECURRENT OVARIAN CANCER**

In recurrent disease, chemotherapy for ovarian cancer is always palliative. Platinum-based chemotherapy may be given as a second-line treatment. Response rates are closely related to the time from primary treatment to relapse. Response rates vary from 25% (in those relapsing within one year) to 60% for those with a disease-free interval of more than two years. For platinum-resistant disease, oral etoposide shows response rates of around 27% and is currently used in patients following failure of first- or second-line platinum-based regimens.

**Cervical cancer**

In general terms, until recently, the first-line therapy for cervical cancer was a choice between surgery and radiotherapy for early stage disease, radiotherapy for advanced disease and chemotherapy was used mainly as
an adjuvant treatment in certain high-risk situations or in the context of recurrent disease. Chemotherapy with combinations such as bleomycin [B], ifosfamide [I] and cisplatin [P] (BIP regimen) was used. In addition to the nephrotoxicity of cisplatinum, bleomycin can cause pulmonary morbidity, while ifosfamide can cause neurological morbidity.

In an almost unprecedented action, the New England Journal of Medicine published on the internet the results of three studies on chemoradiation in cervical cancer in advance of their publication in the journal itself.7–9 Following this, the National Cancer Institute of the National Institutes for Health in Washington, USA, issued a clinical announcement stating that ‘strong consideration’ should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer.

Taken together, the results of five trials involving almost 2000 women with stage I–IV cervical cancer show a 30–50% reduction in the relative risks of relapse or death. These results do, however, appear to come at the price of increased morbidity, such as bowel toxicity, which may require bowel resection and has in some cases resulted in death. The balance between the improved outcome versus increased morbidity is the subject of debate in the UK, although many gynaecological oncology centres have included chemoradiation in their treatment protocols for the management of cervical cancer.

**Endometrial cancer**

Unlike patients with epithelial ovarian cancer, the majority of those with endometrial cancer present with early stage disease. Treatment for this group is surgical, with total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings and pelvic lymphadenectomy forming part of the staging procedure.

Currently, prognostic factors such as tumour grade, depth of myometrial invasion, lymph node involvement and peritoneal cytology are used to determine the need for adjuvant therapy. This takes the form of radiotherapy, either to the vaginal vault or pelvis. There is no evidence that such treatment prolongs survival.

Several chemotherapeutic approaches have been investigated in endometrial cancer in attempts to improve survival.

Progestogen therapy using drugs such as medroxyprogesterone acetate (MPA) and megestrol have shown response rates of up to 30%, but without evidence of increased survival.

Both platinum- and paclitaxel-based drug combinations have shown similar response rates but, again, these have not translated into improved survival.10,11
Vulval cancer

Where possible, the management of vulval cancer is usually surgical in the first instance, with adjuvant radiotherapy in situations where the excision margin is incomplete/inadequate on the vulva and/or the inguinal/pelvic lymph nodes are involved (see Chapter 5).

Chemotherapy, using 5-fluorouracil, cisplatin or both, in combination with radiotherapy, has been used in patients unfit for surgery or in those in whom exenterative surgery would have to be performed in order to excise all tumour. Using this approach response rates of 50–90% have been reported. In cases where complete response has been achieved, some authors suggest that surgical excision of the primary tumour site is not necessary.\(^{12}\)

This approach has led to interest in preoperative treatment for patients with extensive tumours in whom radical primary surgery would be required in order to remove all tumour. By giving chemoradiation preoperatively, several studies have shown that the need for radical surgery decreases, for example leading to preservation of the anal sphincter and avoiding the necessity for major plastic reconstructive procedures.\(^{13}\)

Rare tumours

GESTATIONAL TROPHOBLASTIC TUMOURS

Gestational trophoblastic tumours are the malignant gestational trophoblastic diseases, complete and partial hydatidiform mole being preinvasive. Comprising invasive mole, choriocarcinoma and placental site trophoblastic tumours, these tumours are important, since the vast majority of patients with these conditions are curable with chemotherapy. Patients are referred for follow-up to centres in Dundee, Sheffield or London.

Certain indications for chemotherapy have been established. These include:

- choriocarcinoma on histology
- serum $\beta$-hCG > 20000 iu/l more than four weeks after evacuation of the uterus
- metastatic disease
- persistent haemorrhage
- static/rising $\beta$-hCG following evacuation of the uterus.

If any of these indications exist, then patients are given chemotherapy based upon their level of risk, low or high. The risk category is calculated using a scoring system that takes many factors into account, including the patient’s age, the $\beta$-hCG level and whether the preceding pregnancy had been molar.
‘Low-risk’ patients are treated with intramuscular methotrexate with folinic acid rescue. The ‘high-risk’ group of patients, together with the small number who develop resistance to methotrexate, are treated with an alternating regimen of etoposide [E], methotrexate [M] and actinomycin D [A] – EMA – and cyclophosphamide [C] and vincristine [O]. The EMA-CO regimen can also be augmented with intrathecal methotrexate in patients with cerebral metastases.

SUMMARY

Ovarian cancer
- Adjuvant therapy recommended for high-risk early stage ovarian cancer.
- For advanced disease, poor five-year survival of around 25%.
- Current adjuvant chemotherapy in advanced disease – carboplatin and paclitaxel.
- Response rates in relapsed disease relate to time since last chemotherapy.

Cervical cancer
- Concurrent cisplatin-based chemotherapy should be considered in all patients who require adjuvant radiotherapy.
- Treatment-related morbidity is likely to be higher in this group.

Endometrial cancer
- Progestogen and platinum-based therapies show response rates of up to 30%.
- No evidence that this translates into prolonged survival.

Vulval cancer
- Good responses to 5-fluorouracil-based chemoradiation regimens.
- Preservation of function and avoidance of extended radical procedures possible using chemoradiation.

Gestational trophoblastic tumours
- Follow-up and treatment via centres in Dundee, Sheffield and London.
- Several indications for chemotherapy.
- If indicated, chemotherapy based on ‘low- or ‘high-risk’ scores.
- High cure rates.

Non-epithelial ovarian tumours
- Chemosensitive tumours often associated with high cure rates.
- Always consider fertility-preserving surgery in women of childbearing age.
NON-EPITHELIAL OVARIAN TUMOURS

The malignant non-epithelial tumours comprise mainly sex cord stromal and germ cell tumours. They generally occur in younger women and, although not common, they form an important group of ovarian tumours because, unlike the epithelial ovarian tumours, long-term survival and cure can often be achieved.

Of the sex cord stromal tumours, granulosa cell tumours may require chemotherapy. Combination therapy with bleomycin [B], etoposide [E] and cisplatin [P] (BEP regimen) is active in this situation.16

The malignant germ cell tumours include dysgerminomas and a group of non-dysgerminomas that includes endodermal sinuses and teratomas. Combination chemotherapy with BEP or cisplatin [P], vinblastine [V] and bleomycin [B] (PVB regimen) allow response rates of around 90% to be achieved.17,18 It is worth restating the recommendation that in young women of childbearing age the initial laparotomy for an ovarian tumour should consider fertility preservation due to the potentially curable nature of some of the non-epithelial ovarian tumours.

References


