31

Basic Oncology including Treatment in Less-resourced Locations

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INTRODUCTION

The treatment of most types of gynecological cancers is complex and often requires multiple modalities of treatment. While surgery is the cornerstone of the treatment of early cervical cancer, ovarian cancer, endometrial cancer and uterine sarcoma, early vulval and vaginal cancer as well as breast cancer, radiotherapy and chemotherapy also play important roles. The surgical approaches have been discussed in Chapters 26, 28–30. This chapter will focus on non-surgical approaches namely radiotherapy, chemotherapy and hormonal therapy.

There are limited facilities for radiotherapy as well as a shortage of trained medical and paramedical personnel to plan treatment and operate these radiotherapy facilities in many of the less-resourced locations. Many of the newer drugs that are used for chemotherapy are either not available or too costly for many less-resourced locations. Fortunately, the availability of generic chemotherapeutic agents has made the use of some of these chemotherapeutic agents possible.

We are aware that the accessibility for both radiotherapy and chemotherapy is limited; however, in middle-income countries many services are available. It is good to find out where the nearest referral facility is, and whether a national cancer control plan exists. If you work in a referral setting, extensive knowledge of adjuvant treatment is necessary. To improve quality of care it is good to write treatment protocols and make sure that every healthcare worker involved is adequately trained and capable.

In this chapter, the general aspects of radiotherapy and chemotherapy will first be described followed by specific details for the treatment of gynecological malignancies and breast cancer. An overview on hormonal systemic therapy in breast cancer is provided in Chapter 30.

RADIOTHERAPY

Radiotherapy exerts its therapeutic effects in the cell by both direct and indirect actions. The direct actions of radiotherapy cause atoms in targeted cells to be ionized, starting a chain of events that results in cell death. The majority of cell damage is by the indirect actions of radiotherapy. Radiation interacts with molecules (like water) resulting in the production of free radicals. These unstable molecules interact with the target molecule and strip electrons and break chemical bonds thus causing cell damage.

Radiotherapy is given in fractions (small doses given over a period of days or weeks). When given in fractions, radiotherapy allows normal irradiated tissues to repair damage and repopulate. In cancer cells, however, re-oxygenation and redistribution of cancer cells into phases in the cell cycle that are more susceptible to radiation occurs, thus causing damage to the cancer cells. Radiotherapy is given either by the older Cobalt 60 machines or the newer linear accelerators.

Radiotherapy is a specialized subject and specific details on how to treat patients with radiotherapy will not be described in this chapter. Side-effects of radiotherapy are sometimes encountered, often with a higher incidence when there is a lack of simulator and computer planning facilities in the less-resourced setting. It is important that clinicians involved in the care of patients with gynecological cancers are able to manage these side-effects. Sometimes patients may live at a distance from the radiotherapy treatment facility. Delayed side-effects

can also occur many months or even years after radiotherapy.

Radiotherapy and chemo-radiation in cervical cancer

Early cervical cancer (stage I to IIA) may be treated by surgery or radiotherapy with equivalent results although the complication rate may be higher with radiotherapy (level of evidence 1)[1]. When surgery for cervical cancer is not available, the patient should be treated with radiotherapy.

Radical radiotherapy

Radical radiotherapy for cervical cancer is given by both external beam radiotherapy and brachytherapy. The target for the external beam radiotherapy in cervical cancer is the primary tumor and pelvic nodes. A dose of 45–50.4 Gy is usually given over 25–28 fractions. Brachytherapy on the other hand involves giving high doses of radiation directly to the tumor using radioactive sources such as Caesium[137], Cobalt[60] or Iridium[192] either by manual or remote after-loading techniques (i.e. by introducing a device loaded with radioactive material into the vagina near the tumor).

Combined chemo–radiation

This has been shown to have superior survival rates when compared with radiotherapy alone and is currently the standard treatment for cancer of the cervix bulky stage IB disease to stage IVA (level of evidence 1)[2–6]. Thirty to fifty per cent improvements in response and survival rates have been observed with this modality when compared to radiotherapy alone in randomized trials. Combined chemo-radiation is not difficult to administer provided there are adequate trained personnel to assess and monitor patients, administer chemotherapy according to the predetermined schedule as well as to treat the patient with radiotherapy. Every effort should be made to incorporate this modality of treatment wherever possible because of the superior survival rates. The side-effects of concurrent chemo-radiation are usually not severe and easily managed in most situations.

Prior to combined chemo-radiation, all patients should have a normal blood count and normal renal function. Although there are a number of options as far as the chemotherapeutic agents are concerned,

cisplatin alone given at a dose of $30 \, mg/m^2$ weekly during the administration of external beam radiotherapy is the best option in low-resource settings. The dosage of cisplatin is low, has minimal toxicity and acts as a radiation sensitizer.

Adjuvant postoperative radiotherapy

Adjuvant postoperative radiotherapy is indicated following radical hysterectomy and pelvic node dissection when there are positive pelvic nodes, the resection margins are close or positive and when there is evidence of microscopic parametrial spread. Adjuvant pelvic chemo-radiation has shown a survival benefit versus radiotherapy alone in this situation[1,6,7].

Patients found to have invasive cancer more than stage IA1 after a simple hysterectomy for presumed benign disease should be given postoperative radiation therapy. In this situation pelvic radiation alone in an increased dose of 48–51 Gy should be given. Chemotherapy is used concurrently as in the previously described protocol.

Endometrial cancer

The primary modality of treatment for endometrial cancer is surgery. Low-risk patients are those who are stage IA grade 1 and 2 endometrioid adenocarcinoma. These patients are at low risk of recurrence and do not need adjuvant radiotherapy.

Intermediate-risk patients are those patients with disease confined to the uterus but with risk factors of recurrence. These risk factors include increased age, lymphovascular space invasion, moderate to poor differentiation and deep myometrial invasion (see Table 3 in Chapter 29). Adjuvant treatment for this group of patients remains controversial. The preponderance of data suggests that external beam radiotherapy does not improve overall survival but provides a small improvement in local control. Vaginal brachytherapy appears equally effective, with an improved quality of life compared to external beam radiotherapy in the high-intermediate-risk group[8].

High-risk patients are those with papillary serous and clear-cell histology and risk factors from the intermediate group (myometrial invasion >50%, stromal invasion of the cervix, lymphovascular space involvement) as well as those with advanced-stage disease (see Table 3 in Chapter 29). Radiotherapy is recommended in this group of patients

after surgery. The role of chemotherapy in these patients remains an area of controversy. When chemotherapy is used, carboplatin and paclitaxel is a commonly used regimen. Some studies have showed an increased progression-free survival in patients who have chemotherapy plus external beam radiotherapy compared to patients who have external beam radiotherapy alone.

Most patients with advanced disease should receive chemotherapy and may benefit from adjuvant radiotherapy. The optimal combination of chemotherapy and radiation therapy is still a subject of research.

In the small proportion of patients in whom surgery is precluded due to co-morbidities, primary radiotherapy is an option (level of evidence 1).

In local vault recurrence following primary surgery, extended beam radiotherapy and/or brachytherapy to the vault is the preferred option. In distant recurrence, the options are either hormonal therapy or chemotherapy.

Sarcomas of the uterus are rare uterine malignancies. The prognosis of patients who have these tumors is poor due to the aggressive nature of the disease. Radiotherapy has been found to increase local control of the disease and improve quality of life.

Hormonal therapy with progesterone is used in distant metastasis and advanced endometrial cancer. Options for progesterone are medroxyprogesterone acetate 200 mg daily orally or megestrol acetate 160 mg daily. The response rate in this group of patients will be in the range of 20%. To avoid thromboembolism a low dose of aspirin (50 mg o.d.) may be added.

Vulval cancer

The primary modality of treatment for vulval cancer is surgery. Wide local excision of the cancer with a margin of 2 cm and uni- or bilateral inguinal femoral lymphadenectomy is the standard treatment for invasive cancer of the vulva in low-resource settings. Unilateral (ipsilateral) inguinal lymphadenectomy is performed if the tumor is located laterally (>1 cm from the midline) of the vulva. For midline tumors and in patients with unilateral lymph node involvement, bilateral inguinal lymphadenectomy is performed. Patients with two or more inguinal metastases or bilateral metastases to the groin nodes should undergo inguinal and pelvic irradiation after primary surgery.

Ovarian cancer

Radiotherapy has a limited role in palliation in selected patients with ovarian cancer. About 5–10% of patients with recurrent ovarian cancer present with vaginal involvement and may have symptoms of vaginal bleeding or discharge as well as perirectal obstruction. Radiotherapy can ameliorate these symptoms[11].

Gestational trophoblastic disease

The mainstay of treatment of choriocarcinoma is chemotherapy. Isolated brain metastases can be treated with radiotherapy. Further details are given in Chapter 27.

Breast cancer

Radiotherapy has an important role in the treatment of early and advanced breast cancer. If the patient needs to be treated with both radiotherapy and chemotherapy, radiotherapy should follow chemotherapy. Hormonal treatment can be administered concomitantly to radiotherapy (see Chapter 30). All patients with early-stage breast cancer and who have had breast-conserving surgery (see Chapter 30) will need whole breast irradiation with 50 Gy in 25 fractions over 5 weeks, 5 days a week and those <50 years of age will need an additional boost of 16 Gy to the tumor bed[12]. In cases of positive axillary lymph nodes the radiation field should include the supraclavicular region as well.

Patients with advanced breast cancer requiring a mastectomy and axillary lymphadenectomy should receive radiotherapy if axillary lymph nodes were found positive during the operation. Radiation should include the chest wall and supraclavicular region at a dose of 50 Gy delivered in 25 fractions, 5 days a week over 5 weeks. The literature shows a significant reduction in local recurrence and an increase in survival for these patients[12]. Radiation of the axilla is only needed if the lymphadenectomy was inadequate (i.e. producing <10 lymph nodes).

Patients with advanced disease, negative lymph nodes but other high-risk features such as tumor size >2 cm or close resection margins will need chest wall irradiation without radiation to the lymphatic regions to increase local control. The dosage and schedule is as described in the previous paragraph.

Patients with advanced disease who require neoadjuvant systemic therapy before operation will

need chest wall irradiation after successful mastectomy and regional lymph node irradiation depending on intraoperative findings. Those who still cannot be operated on after neoadjuvant systemic therapy should receive chest wall irradiation including axillary and supraclavicular lymph nodes.

Side-effects of radiotherapy

Minor side-effects of radiotherapy are skin changes and fatigue. Anemia is an important cause of fatigue and should be treated. Depression can exacerbate feelings of fatigue. Side-effects can occur during radiation for pelvic malignancies due to the effects of radiotherapy on the organs close to the areas being irradiated, namely colon and rectum (radiation proctitis), bladder (radiation cystitis) and small bowel (radiation enteritis). Lymphedema of the breast and arm, as well as lung and heart side-effects (radiation pneumonitis and fibrosis, dilatative cardiomyopathy) can occur with radiation for breast cancer. Radiation-induced side-effects may be immediate, occurring during the treatment, or delayed, occurring months or even years later.

Managing side-effects of radiotherapy

The most common side-effect encountered in radiotherapy for genital cancers is due to radiation to the rectum and sigmoid colon. Patients present with symptoms of proctitis including bleeding per rectum and diarrhea. Most patients have mild symptoms that can be treated with simple measures.

Patients with diarrhea should be adequately hydrated by drinking at least 8–12 cups of clear fluids per day. Eating five to six small meals rather than three large meals is helpful. Foods that are low in fiber, fat and lactose are recommended. Patients are also advised to avoid oily food, milk and dairy products and foods that cause production of gas like beans.

Repeated episodes of diarrhea can cause irritation to the skin around the anal area. Toilet paper is not recommended. Instead, squirting water after bowel movements is advised to clean the anal area. Warm water-sitting baths are soothing. Medication that can be prescribed for diarrhea include dioctahedral smectite (Smecta®) 3 g 6-hourly or loperamide (Imodium®) daily or as necessary.

Rectal bleeding due to radiation proctitis can be treated with hydrocortisone enema 100 mg/60 ml once to twice daily until the bleeding stops. In less-resourced settings application of 4% formalin has been found to be effective. The options that have been described are instilling four separate 20 cc aliquots into the rectum with total mucosal contact of 20 min or performing a rigid sigmoidoscopy and applying a gauze soaked in 4% formalin in contact with the mucosa for 4 min, repeating the procedure until the bleeding stops[9].

Patients with significant per rectal bleeding should undergo endoscopic evaluation of the rectosigmoid and descending colon to exclude other causes of bleeding such as arterial venous malformations, inflammatory bowel disease and malignancy. A specific bleeding point if identified, can be coagulated.

Rare complications of radiotherapy include sigmoid stricture and vesico-vaginal or recto-vaginal fistulae. Patients with rectosigmoid stricture present with progressive bouts of constipation and in later stages with abdominal pain, distention and vomiting. When conservative measures fail, surgery is necessary.

Recto-vaginal fistulae presents with foul smelling discharge or feces being discharged per vagina. The surgical management of these complications requires considerable surgical judgment and an experienced surgeon should be involved in the assessment and treatment of these problems as operating on irradiated bowel is fraught with potential complications.

Radiation-induced small bowel damage is more difficult to diagnose and manage. Patients may present with moderate to severe bowel symptoms, and small bowel obstruction may sometimes occur. The initial management will involve intravenous hydration and correction of electrolyte imbalance. Nasogastric suction is useful in patients with nausea and vomiting and dilated small bowel loops. Conservative management may result in improvement and resolution of partial obstruction in some patients. Good surgical judgment is important when surgical intervention is contemplated and the treating surgeon must be experienced in managing these problems.

Patients with radiation cystitis may present with frequency, dysuria, hematuria and suprapubic pain. The incidence has been reported as approximately 6% with the majority of patients having minor symptoms. Most patients with minor degrees of hematuria resolve with antibiotics. Persistent hematuria will require cystoscopy to exclude recurrent cancer or a second primary tumor. Severe bleeding

and the passage of clots will require insertion of a large 3-way Foley's catheter and performing continuous bladder irrigation. Monitoring the inflow and outflow of infused fluids and maintaining drainage is important as there are risks of bladder distention and rupture.

Rarely, hematuria does not respond to bladder irrigation and other measures may need to be considered. A 1% solution of Alum (50 g potassium aluminum sulfate in 5 liters of distilled water) to run intravesically at 3–5 ml/min and increasing to a maximum of 10 ml/min if the returning fluid from the bladder is not clear is an option. The irrigation must be continued for 6 h after the bleeding has stopped.

Formalin is effective in stopping intractable hematuria but should only be used as a last resort as there is a risk of complications including bladder contracture, ureteral fibrosis and delayed fistula formation. Ureteral reflux and bladder perforation must be excluded by cystogram prior to using formalin. A 4% solution is used and the bladder is filled to capacity for 23 min. As the procedure is painful it should be conducted under general anesthesia.

Patients with cervical cancer and parametrial involvement may present with hydronephrosis and sometimes complete obstruction and anuria due to blockage of the ureters by parametrial tumor extension. Sometimes patients with a partially obstructed ureter may develop complete obstruction with the initiation of radiotherapy, as the radiotherapy can cause tissue edema that completely blocks off partially obstructed ureters.

In patients with hydronephrosis, the ideal management is cystoscopy and stenting of the ureters by a urologist or surgeon with the necessary experience. Ureteric stents can be expensive and the necessary trained personnel to perform these procedures are not always available. An alternative is to perform a nephrostomy and drain the urine percutaneously under ultrasound guidance. This procedure can salvage existing renal function while radiotherapy is initiated. If possible a retrograde stenting of the ureter should be carried out with radiological assistance at some stage later.

Sometimes radiotherapy will cause obstructed ureters to 'open up' due to shrinkage of tumors. When this happens after complete obstruction, the patient may go into a state of diuresis for many days. Intravenous hydration will be necessary and close attention to managing fluid balance and electrolyte imbalances is important in this situation.

The most frequent side-effects of radiotherapy in breast cancer are skin changes (i.e. redness, swelling, which is called radiodermatitis or ulcera). When this occurs, it is important to instruct the patient to keep the area of radiation dry at all times. Local measures for radiodermatitis include application of dexpanthenol ointment. If symptoms are severe, radiation might have to be temporarily stopped until radiodermatitis subsides. Lymphedema of the breast and arm may cease on its own after 6–12 months, otherwise physiotherapy (i.e. lymphatic drainage) might be needed. The patient herself or a female family member can be taught how to do that regularly.

Other complications are more severe, but fortunately rare, such as cardiomyopathy or pulmonary fibrosis. Patients with chest wall irradiation, however, experience a higher rate of these complications.
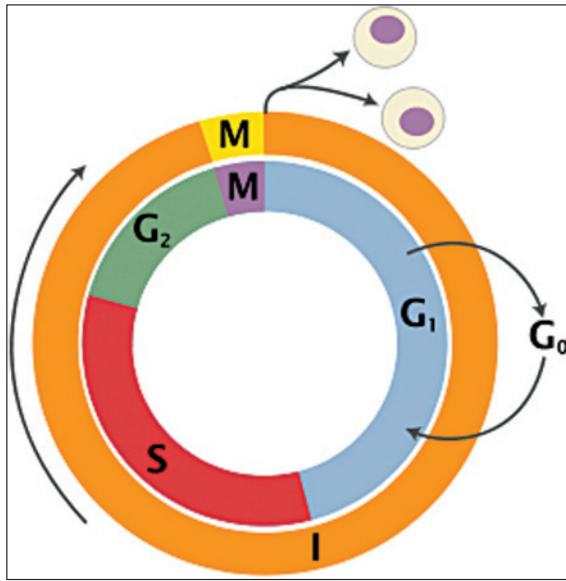
CHEMOTHERAPY

Cancer is characterized by unregulated growth. This unregulated growth is caused by the loss of two cell control mechanisms that occur in normal cells. Firstly, there is a loss of the normal cell cycle regulation control and secondly there is failure of normal programmed cell death (apoptosis).

It is useful to have an understanding of the normal cell cycle. There are four phases as described below (Figure 1).

1. *M-phase* Chromosome division occurs (mitosis) yielding two daughter cells.
2. *G-1 phase* Specialized functions of cell types are fulfilled and the cell's machinery is prepared for DNA synthesis. Cellular activities, protein and RNA synthesis and DNA repair occur in preparation for cell division; *G-1 cells can terminally differentiate into G-0 (non-cycling cells) or re-enter the cell cycle after a period of quiescence*.
3. *S-phase* New DNA is synthesized (replication of existing strand).
4. *G-2 period* A short phase when the cell's nucleus is being organized for mitosis. The cell contains haploid number of chromosomes and twice the DNA of a normal cell; RNA and protein are synthesized.

Normal and cancer cells are sensitive to chemotherapy during the active cell cycling period and

Figure 1 Schematic of the cell cycle. Source: Wikipedia. Illustration by Zephyris (Richard Wheeler)

less sensitive to chemotherapy during the resting or G-0 phase.

The growth of tumor cells displays a growth pattern called Gompertzian growth. There is an initial pattern of rapid proliferation followed by progressive delay in doubling time. The time required to double the tumor volume increases as the tumor volume increases. The resulting growth curve is sigmoid. When the tumor is small, in the initial phase of the growth curve, the relatively small number of tumor cells divide and grow slowly. The tumor then enters a rapid growth phase and finally plateaus into a slower rate of growth when the tumor is large and able to kill the host.

A large tumor is more resistant to chemotherapy because the proportion of cells that are actively dividing are small and more cells are in the non-proliferating G-0 phase (when they are less sensitive to chemotherapy). Another cause of resistance is inadequate doses of chemotherapeutic agents as the tumor outgrows its blood supply. The doubling times can vary according to the tumor type and can range from 1–6 months. For more information on the cell cycle, please refer to: http://en.wikipedia.org/wiki/Cell_cycle

Combination chemotherapy

Gynecological cancers are often treated with combination chemotherapy. In general, combinations

achieve better chemotherapeutic effects compared to single drugs by two main mechanisms. Firstly, by using a number of drugs with different toxicities, increased anti-tumor effects can be obtained with limitation of the severity of individual drug toxicities. Secondly, as the different drugs used in combination chemotherapy have different mechanisms of action, the risk of drug resistance developing is decreased. Chemotherapy is used in a number of ways in gynecological cancers:

- *Induction chemotherapy* is used up-front in certain situations in patients with metastatic disease where chemotherapy is the best option (e.g. choriocarcinoma).
- *Adjuvant chemotherapy* is used after initial surgery when the likelihood of recurrence is high (e.g. in ovarian cancer after primary surgery).
- *Neoadjuvant chemotherapy* is the term used when chemotherapy is used prior to surgery (or radiotherapy) to decrease the size of the tumors with the aim of decreasing the morbidity of surgery. It is being increasingly used in patients with advanced ovarian cancer who are poor candidates for immediate surgery due to co-morbidities.
- *Palliative chemotherapy* is used when the patient has an advanced malignancy that is incurable to improve symptoms.

Dose

In the administration of chemotherapy, the right dose of drugs required must be calculated for each individual patient. Calculations are based on:

- The patient's weight in kilograms
- The body surface area (BSA) in m². This is a more difficult calculation but many internet tools are available, e.g. http://www.miniweb tool.com/bsa-calculator/metric/
- The area under the curve (AUC), see the paragraph on epithelial ovarian cancer below.

It is very important to calculate the appropriate dose for each patient: underdosing will reduce the effectiveness of the therapy, while overdosing may increase toxicity. For this reason it is a good practice to have two people do the calculations independently and then compare the results.

Toxicity

All chemotherapeutic drugs have toxicities. The clinician must be aware of the toxicities of

commonly used chemotherapeutic agents used in gynecological cancer. Toxicities may be classified according to the common toxicity criteria (CTC) scale by the World Health Organization (WHO). Specific conditions and symptoms may include biochemical laboratory values or descriptive comments for each level, but the general classification is:

1. Mild
2. Moderate
3. Severe
4. Life-threatening
5. Death.

Further details can be obtained at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Hematological toxicities

Hematological toxicities are among the most common toxicities encountered and are seen with most of the chemotherapeutic agents. *Leukopenia* usually occurs 10–14 days after treatment with most chemotherapeutic agents and may persist for 3–10 days. When the patient is leukopenic, she is at risk of infections. Severe neutropenic septicemia is a life-threatening condition and prophylactic antibiotics like ciprofloxacin plus amoxicillin/clavulanate may be considered.

Thrombocytopenia is the other hematologic complication that can occur with chemotherapy. The onset as well as recovery of thrombocytopenia usually slightly lags behind that of leukopenia. There is a risk of hemorrhage when the platelet count drops <50,000/m^3, with the risk of serious bleeding occurring when the platelet count decreases to <10,000/m^3. Prophylactic platelet transfusion should be considered when the platelet count drops to <10,000 U/l. If leukopenia or thrombocytopenia is significant, there may be a need to delay the next course of chemotherapy and decrease the dosage of subsequent courses of chemotherapy.

Anemia often occurs with chemotherapy and can contribute to fatigue. Mild anemia is usually well tolerated by most patients and transfusion of blood is not recommended due to the risk of blood-borne infections. When anemia is severe, blood transfusion may be necessary. Ferrous sulfate should be prescribed prophylactically to all patients on chemotherapy to decrease the incidence of anemia. Blood counts should be carried out at the expected leukocyte nadir as well as prior to administration of chemotherapy.

Table 1 Dose adjustment for carboplatin–paclitaxel in leukopenia and thrombopenia (count at nadir)

Platelets	WBC count	
	>2.5 × 10^9	<2.5 × 10^9
≥75 × 10^9/l	100% starting dose	Delay 1 week and reduce AUC of carboplatin to 4, 75% of paclitaxel dosage
<75 × 10^9/l	Delay 1 week then reduce AUC to 4, paclitaxel 100%	Delay 1 week then reduce AUC to 4, 75% of paclitaxel dosage

WBC, white blood cell; AUC, area under the curve

Some drugs, e.g. carboplatin, have cumulative hematological toxicity and progressive toxicity occurs as the patient is given more cycles of chemotherapy. Dose reduction of chemotherapeutic agents may be required in this situation. Other agents like paclitaxel do not have cumulative toxicity and can often be given for many cycles without dose modification.

Table 1 gives an example of dose reduction for the carboplatin/paclitaxel regimen, commonly used as adjuvant treatment for ovarian cancer, uterine cancer as well as recurrent cervical cancer based on leukocyte counts and platelet counts at the nadir. The counts must have returned to normal levels prior to administration of the next course of chemotherapy.

Febrile neutropenia

Febrile neutropenia is defined as an oral temperature >38.5°C or two consecutive readings of >38.0°C for 2 h and an absolute neutrophil count <0.5 × 10^9/l or expected to fall to <0.5 × 10^9/l[13]. Febrile neutropenia is a serious complication of chemotherapy and patients must be advised of this potential complication and told to seek medical help if febrile or unwell while on chemotherapy.

There are a number of potential sources of infection when a patient has febrile neutropenia. The sources of infection can be the skin (*Staphylococcus epidermis* or *S. aureus*) or gastrointestinal tract (*Escherichia coli* or *Klebsiella pneumoniae*). When there is partial or complete obstruction of the gastrointestinal tract, overgrowth of gut flora may occur and these bacteria may enter the bloodstream causing septicemia. The urinary tract is another

potential source of infection. Tumor invasion to the bladder and urinary tract and urinary tract obstruction can predispose to infection from the urinary tract. Breakdown of mucosal barriers, wound infection from surgery as well as anemia and poor nutrition are also factors that can predispose the cancer patient to infection.

General assessment of patients with febrile neutropenia will include temperature, pulse and heart rate. The patient must be carefully evaluated clinically for the source of infection by assessing the oropharynx and lungs. In addition, intra-abdominal pathology as well as other possible sites of infection like pelvic abscess, post-surgery wound infection and skin infection at sites of intravenous access must be excluded. A urinalysis and culture and blood cultures must also be performed.

Manifestations of infection may be subtle in patients who are neutropenic with only fever, sometimes mild as an initial presenting complaint. A hemodynamically unstable patient should be admitted in an intensive care unit if available and aggressively treated with intravenous fluids and broad-spectrum antibiotics after the appropriate cultures (blood cultures, sputum, urine, wounds) for antibiotic sensitivity are obtained. A central venous (CVP) line must be inserted, the patient catheterized and urine output monitored. Vasopressor drugs may be used as necessary to maintain the blood pressure and maintain renal profusion.

The best antibiotic to use initially in the less-resourced setting is a third-generation cephalosporin such as ceftazidime and aminoglycoside (gentamicin, amikacin). If there is a suspected intra-abdominal source of sepsis, metronidazole should be added. Subsequent treatment will be guided by the results of blood and other culture results. If cultures are negative and the patient has recovered, broad-spectrum antibiotics must be continued until the patient is afebrile for 72 h and the neutrophil count has risen to >1000/μl.

If fever persists after > 5 days treatment of broad-spectrum antibiotics, and cultures are negative other etiological agents must be considered such as fungal infections.

Nausea and vomiting

This is one of the most commonly encountered side-effects of chemotherapy. The degree of nausea and vomiting depends on the individual drugs or

Table 2 Emetogenicity of several chemotherapeutic drugs

Emetogenic potential	Drugs/regimens
Mildly emetogenic	Paclitaxel
	Bleomycin
	Vinblastine
	Vincristine
Moderately emetogenic	Carboplatin
	Doxorubicin
	Cyclophosphamide
	Etoposide
	Methotrexate
Highly emetogenic	Cisplatin (high dose)
	Cyclophosphamide (high dose)
	Ifosfamide
	EMACO

EMACO, etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine (Oncovin®)

combinations used. The serotonin antagonists were a major advance in the prevention of nausea and vomiting. Unfortunately the costs of serotonin antagonists are high and they may not be available for use in the low-resource setting.

All patients on chemotherapy should receive anti-emetic pre-medication. The type of anti-emetic should depend on the emetic potential of the drugs used (Table 2).

Dexamethasone, lorazepam and metoclopramide are widely available and relatively inexpensive. Intravenous (IV) dexamethasone 20 mg should be administered 15–20 min before the chemotherapy. IV lorazepam 1–2 mg aids in potentiating the anti-emetic efficacy of dexamethasone. IV metoclopramide 2 mg/kg should also be prescribed. The serotonin antagonists (ondensetron and granisetron) when available should be restricted to severe and moderately severe chemotherapy.

One of the most emetogenic drugs is cisplatin when given in doses of >75 mg/m². Vomiting occurs 2–3 h following administration of the drug with the peak at 5–6 h. Cisplatin and carboplatin are associated with delayed emesis. Those patients on drugs that may cause delayed emesis should be treated with oral dexamethasone 8 mg twice a day for 2 days followed by 4 mg twice a day for a further 2 days. In addition patients should also receive metoclopramide 0.5 mg/kg orally 6-hourly for 2 days.

Alopecia

Alopecia occurs with drugs like cisplatin, paclitaxel and doxorubicin as well as other anthracyclines. Some of the other chemotherapeutic drugs may cause milder degrees of hair loss. Although not life-threatening, alopecia is very distressing to most patients. Patients should be warned of this side-effect prior to administration of these drugs. They should be reassured that the hair will grow back on completion of the chemotherapy. When wigs are available, patients should be advised to obtain a wig to match their normal hairstyle prior to the hair loss.

Neurotoxicity

Neurotoxicity occurs after drugs like cisplatin and paclitaxel. Sensory loss can occur in the peripheries and can be progressive and sometimes permanent. Patients should be warned of the possibility of this happening and assessed periodically throughout the treatment as well. Patients with sensory neuropathy should be advised to exercise caution when holding objects as these objects may be accidently dropped due to loss of sensation in the hands and fingers.

Table 3 Regimen for maintaining hydration and urinary output during administration of cisplatin chemotherapy

	Fluid	Volume	Drug	Time
1.	Normal saline	1 litre		1 h
2.	Normal saline	1 litre		1 h
3.	Normal saline	250 ml		15 min
4.	Normal saline	1 litre	Cisplatin 75 mg/m^2	2 h
5.	Normal saline	1 litre	1 g MgSO$_4$	2 h
6.	Normal saline	1 litre	20 mmol KCl	6 h

They should wear proper shoes all the time. In addition patients should be advised to have a small light on during the night as well as to remove rugs, electric wires across the floor, etc. to prevent falls especially when using the toilet in the night.

Genitourinary side-effects

Genitourinary side-effects occur with some drugs. Cisplatin is a drug that can cause nephrotoxicity. Prior to administration of cisplatin, normal renal function must be confirmed.

It is important to maintain adequate intravenous hydration and ensure good urinary output during administration of cisplatin chemotherapy. The regimen shown in Table 3 is often used to maintain hydration and urinary output during administration of cisplatin chemotherapy.

Hemorrhagic cystitis

Hemorrhagic cystitis can occur with ifosfamide. Prevention of this complication is achieved by maintaining a high urine output as well as administering mesna with ifosfamide.

Doxorubicin plus ifosfamide is a chemotherapeutic regimen that is sometimes used in the treatment of sarcoma of the uterus. The regimen is described in Table 4, illustrating how mesna and IV fluids are used to decrease the risk of hemorrhagic cystitis.

Skin changes

Skin changes like pigmentation and darkening of the skin as well as nail abnormalities are sometimes seen with a number of chemotherapeutic agents.

Table 4 Regimen with mesna and intravenous fluids to decrease the risk of hemorrhagic cystitis

	Fluid	Volume	Drug	Time
1.	Normal saline	50 ml	Doxorubicin 40 mg/m^2	IV push
2.	Normal saline	100 ml	Mesna 1 g/m^2	1 h
3.	Mannitol	200 ml	20% Mannitol	3 h
4.	Dextrose saline	1 litre	1/3 of ifosfamide 5 g/m^2 1/3 of mesna 5 g/m^2	8 h
5.	Dextrose saline	1 litre	1/3 of ifosfamide 5 g/m^2 1/3 of mesna 5 g/m^2	8 h
6.	Dextrose saline	1 litre	1/3 of ifosfamide 5 g/m^2 1/3 of mesna 5 g/m^2	8 h
7.	Dextrose saline	1 litre	Mesna 3 g/m^2	8 h

Mucositis

Mucositis can occur with methotrexate, 5-fluoro-uracil, dactinomycin, doxorubicin, mitomycin C and vincristine. The onset of mucositis is 5–7 days following administration and will usually resolve spontaneously within 2–3 weeks. Good oral hygiene is important.

Extravasation

Extravasation is a serious complication of a number of chemotherapeutic agents. Skin necrosis can occur with some drugs like doxorubicin, actino-mycin D, mitomycin C, etoposide and vincristine when extravasation occurs.

Prevention is obviously best, and can be ensured by a number of simple measures. Firstly, choose large distal veins in the forearm, avoiding veins in the joints and antecubital fossa as well as veins in which there has been access or attempted access in the preceding 24 h. Secondly, ensure that the intravenous line is free flowing. Prior to adminis-tering the chemotherapeutic drug, the IV lines should be flushed slowly with 100 ml of normal saline. Initial administration of the chemotherapeu-tic drug should be slow, at 1–2 cc per min paying attention to the patient's complaints at the same time. While administering chemotherapy, the drip site must be continually monitored for redness, swelling or leakage.

When extravasation occurs, the chemothera-peutic drug must be stopped at once. There are specific antidotes for some drugs. For doxorubicin extravasation, dilute hydrocortisone 100 mg per ml with 5 ml of saline and inject 1–2 ml through the IV line and inject the remaining solution into the extravasation site via 2 or 3 injections. Apply cold compress.

For dactinomycin extravasation, prepare a solu-tion of sodium thiosulfate by mixing 4 ml of 10% sodium thiosulfate with 6 ml of sterile water for in-jection. Inject 6 ml through the existing IV line and inject 2 ml subcutaneously via multiple injections. The subcutaneous injection can be repeated hourly over the next few hours. Apply cold compress.

For vincristine and etoposide extravasation, the antidote is hyaluronidase; 1–6 ml of a 150 U/cc solution is injected subcutaneously via multiple injections, repeating hourly over the next few hours. A warm compress is advised in this situation.

Hypersensitivity

Hypersensitivity can occur with a number of chemotherapeutic drugs like etoposide, cisplatin, carboplatin, doxorubicin, cyclophosphamide/ ifosfamide, melphalan, methotrexate, paclitaxel, 5-fluorouracil and bleomycin. Most patients will present with wheezing or rash. Rarely, serious complications like angio-edema and hypotension can occur. Hypersensitivity is treated by discon-tinuing treatment at once, maintaining an IV line with intravenous normal saline, antihistamines, corticosteroids, vasopressors and bronchodilators.

The drug with the highest incidence of hyper-sensitivity is paclitaxel. It is now possible to greatly decrease the incidence of hypersensitivity to pacli-taxel with prophylactic treatment with dexa-methasone, diphenhydramine (antihistamine) and cimetidine or ranitidine before administration of the drug.

Paclitaxel is often used together with carboplatin as adjuvant treatment of ovarian cancer as well as some other gynecological cancers. The schedule below describes how this drug combination is administered with adequate pre-medication to decrease paclitaxel hypersensitivity:

Carboplatin/paclitaxel regimen for epithelial ovarian cancer
1. Dexamethasone 20 mg IV in 100 cc normal saline (N/S) over 15 min
2. Phenergan 12.5 mg IV over 30 min in N/S
3. Ranitidine 50 mg slow bolus
4. Granisetron 3 mg IV bolus
5. Paclitaxel in 100 ml N/S to run over 3 h 175 mg/m^2
6. Carboplatin in 500 ml N/S AUC of 5 to run over 60 min

When hypersensitivity to a drug occurs, it is best not to use the same drug again. There are certain situations, however, where the drug in question may be the best option for an individual patient, due to reasons like a good response to treatment with that particular drug or lack of other good alternatives. When this occurs, a careful assessment must be carried out of the benefits of the particular treatment causing hypersensitivity versus the risk of hypersensitivity reaction. If it is felt that the drug that has caused hypersensitivity is still the best option, desensitization may be carried out by administering SoluMedrol 100 mg IV every 6 h for 24 h prior to paclitaxel administration.

Pulmonary side-effects

Bleomycin is associated with interstitial pneumonitis which can lead to pulmonary fibrosis. The risk of this complication is dose related. Methotrexate hypersensitivity can result in interstitial pneumonitis and vasculitis.

Other side-effects of chemotherapeutic agents include diarrhea, esophagitis, gastritis and cardiac side-effects (epirubicin).

Waste management and workplace safety

As was explained earlier, chemotherapeutic drugs are toxic substances. They are highly hazardous to exposed staff and to the environment. Health workers administering chemotherapeutic drugs should be adequately trained. Pregnant health workers should not deal with chemotherapeutic drugs as they are teratogenic. Other staff should wear gloves while preparing, administering and disposing these drugs and other items in contact with these drugs such as syringes, gloves, intravenous lines. These items cannot be disposed of in an ordinary waste pit but need to be kept secure and be burned separately. The following needs to be in place when chemotherapy is being administered:

- Treatment protocols, protocols for side-effect management, emergency protocols for extravasation.
- Waste management plan (e.g. storage in separate leak-proof containers, labeling, separate incineration at high temperatures or return to supplier).
- Safety guidelines for staff (e.g. training, protective gear, spillage protocol, decontamination).

These protocols and plans often already exist at national or tertiary level and you should identify facilities where you can be trained in these important areas described above.

Chemotherapy in gynecological and breast cancer

Epithelial ovarian cancer

Surgery is the cornerstone for the primary treatment of ovarian cancer. Many patients will benefit from adjuvant chemotherapy following surgery. The 10-year survival in patients with FIGO stage IA–B, grade 1 and 2 tumors is around 90% after an optimal surgical staging alone. No additional benefit in progression-free or overall survival was observed with adjuvant chemotherapy in *optimally* staged early-stage ovarian cancer (see Chapter 28). All other patients will benefit from six courses of adjuvant chemotherapy administered 3-weekly after primary debulking surgery.

The most widely used regimen is a combination of paclitaxel and carboplatin. It is easy to administer and the side-effects are manageable. Paclitaxel used to be an expensive drug but the availability of several generic forms of the drugs has now made it possible to use in the less-resourced setting. If paclitaxel is not available, patients should be treated with carboplatin alone.

Dosage of carboplatin is best calculated according to the Calvert formula based on 24-h collection of urine for creatinine clearance and doses. Target doses of AUC of 5 or 6 are used. AUC stands for *area under the curve.*

Dose (mg) = target AUC × (creatinine clearance + 25)

For more information on creatinine clearance please see: http://en.wikipedia.org/wiki/Renal_function. When creatinine clearance is not available the following formula may be used:

Carboplatin 300–400 mg/m^2 over 30 min

Cycles are given once in 3 weeks with clinical assessment plus CA-125 levels (if available and elevated prior to surgery), full blood count, renal and liver function tests prior to each course of chemotherapy.

Neoadjuvant chemotherapy is being increasingly used selectively in patients with a presumptive diagnosis of ovarian cancer. The diagnosis is usually made after clinical examination, tumor markers (CA-125), imaging (CT scan is ideal) and tissue biopsy. Neoadjuvant chemotherapy is indicated in ovarian cancer patients who are at high risk for complications from surgery due to advanced disease as well as co-morbid factors. Three courses of carboplatin/paclitaxel are given. Surgery is then carried out in patients who respond to the chemotherapy (see Chapter 28).

The management of recurrent ovarian cancer is more complex. Once recurrence occurs, the disease is incurable, but good palliation, improvement of quality of life and possibly improvement of lifespan is possible with further treatment. The key determining factor is the platinum-free interval. This is the time between completion of

chemotherapy with carboplatin and diagnosis of recurrence. Patients should not be treated based on raised CA-125 alone in the absence of clinical or radiological evidence of recurrence.

If the platinum-free interval is ≤6 months, the patient is considered platinum resistant and the prognosis is poor. Patients are treated with single-agent chemotherapy. There are a number of options of chemotherapeutic agents available to treat patients in this setting. Unfortunately, many of the drugs used in this situation are expensive. In the low-resource setting, one of the options for platinum-resistant disease is oral etoposide 50 mg twice a day for 7 days every 21 days, increasing to 10 days and then 14 days if toxicities are manageable[10]. The likelihood of response is in the region of 20–25%. Another option is weekly paclitaxel at 80 mg/m^2, giving good palliation with manageable toxicity.

In platinum-sensitive disease, there is a direct relationship between the duration of the platinum-free interval and the response to further treatment, with a better response with longer platinum-free interval. In platinum-sensitive disease (with platinum-free interval ≥12 months), patients must be carefully assessed clinically as well as radiologically by CT scans. Selected patients may benefit with repeat surgery, a surgical procedure called secondary cytoreduction. This procedure will only benefit patients if the disease can be completely resected at surgery, therefore careful selection of suitable patients is necessary. The surgery should only be undertaken by surgeons with the necessary experience, expertise and skills. If complete resection of the tumor is not achieved at an attempt at secondary cytoreduction, the patient will have the morbidity of the second surgery with no clinical benefit. There are additional criteria before embarking on secondary cytoreductive surgery – the patient must have been optimally debulked at the primary surgery, the recurrence should be isolated, with no evidence of carcinomatosis, and the surgeon should be confident that a complete resection of the recurrent tumor could be achieved.

In recurrence of ovarian cancer in platinum-sensitive disease, the patient may be retreated with platinum-based chemotherapy. Patients who have had secondary cytoreduction should receive the chemotherapy after recovery from the surgery. Patients who are not candidates for secondary cytoreductive surgery should receive chemotherapy when they have signs or symptoms of the recurrence.

The best option in this situation is six courses of paclitaxel and carboplatin. If paclitaxel is not available, then carboplatin alone can be used. A dose reduction of 80% of the calculated dose is used when these patients are treated with second-line chemotherapy.

Germ cell tumors

Germ cell tumors are generally chemosensitive. FIGO stage IA dysgerminoma and FIGO stage IA immature teratoma grade 1 do not need chemotherapy after surgery. All other germ cell tumor histological types and stages will need chemotherapy.

The standard treatment is the BEP regimen[14,15] (bleomycin 30 units per week, etoposide 100 mg/m^2/day for days 1–5, cisplatin 20 mg/m^2/day for days 1–5 for 3–4 cycles. It is a toxic regimen. Blood parameters need to be monitored closely and many patients will need dose reduction. See Appendix 4 of Chapter 28.

Sex cord stromal tumors

Adjuvant chemotherapy may be considered for high-risk stage I patients (stage IC, poorly differentiated, heterologous elements as well as those with more advanced disease). Chemotherapy with paclitaxel and carboplatin in the standard fashion as described previously is the currently preferred option.

Endometrial cancer

The role of chemotherapy in endometrial cancer is controversial and has been discussed earlier in this chapter as well as in the Chapter 29 on cancer of the uterine corpus. In addition to its role (controversial) in adjuvant disease, chemotherapy is also used in the recurrent setting when metastatic disease is present.

For recurrent disease, the preferred option is paclitaxel/carboplatin administered in the same way as in ovarian cancer. When paclitaxel/carboplatin is not available, another option for chemotherapy to consider is doxorubicin 60 mg/m^2 plus cisplatin 50 mg/m^2 every 3 weeks.

Carcinosarcoma of the uterus

These are aggressive tumors which have a poor prognosis in spite of treatment. Following surgery, chemotherapy with paclitaxel and carboplatin is the

first option to consider. Doxorubicin and ifos-famide with mesna is another regimen that is used in sarcomas of the uterus.

Gestational trophoblastic disease

Chemotherapy is very effective in gestational trophoblastic disease. Further details are given in Chapter 27.

Breast cancer

See Chapter 30 for the specific indications for chemotherapy in breast cancer. The aim of treatment for patients with stage I–III disease is cure and they should be treated with combination therapy even at the cost of toxicity. Patients with stage IV disease are treated with as little therapy as needed since they cannot be cured and the aim of therapy is solely to improve the quality of life of the patient with as few side-effects as possible.

Newly diagnosed stage I–III breast cancer may be treated on an out–patient basis. The gold standard for early breast cancer is a taxane-based regimen, which is slightly superior to anthracycline-based regimens for nodal-positive disease [relative risk (RR) 0.86 for distant recurrence and 0.87 for mortality[16]] (level of evidence 1a). However, the former may not be available in many resource-limited settings. The Breast Health Global Initiative (BHGI) recommends their use only for areas with an enhanced level of resources (see Chapter 30).

There are no well-designed studies on the best drug regimen in low-resource settings. In many places the choice of regimen will depend on the availability of drugs and associated toxicity. The Early Breast Cancer Trialist Collaborative Group (EBCTG) is carrying out meta-analyses on all randomized controlled trials (RCT) on adjuvant treatment since 1985. The latest update has included 100,000 women in 123 RCT and compared the following[16]:

- Taxane vs non-taxane-based regimens.
- Any anthracycline-based regimen vs CMF (cyclophosphamide, methotrexate and 5-fluorouracil).
- Higher vs lower anthracycline dosage.
- Polychemotherapy vs no chemotherapy.

The following results were produced for the regimen quoted below[16]:

- CMF and AC were equivalent in outcomes (recurrence, mortality) and superior to no chemotherapy. They led to a reduction in mortality rates by 20–25%.
- CEF and CAF had similar outcome rates and added an extra 15–20% reduction in mortality rates.
- Taxanes added to anthracycline-based regimen improved outcomes slightly but significantly.

The classical regimen in breast cancer is CMF. It has relatively few side-effects and the agents are often available in resource-poor settings. Where available anthracycline-based regimens should be used. Regimens with different dosages of anthracyclines (e.g. $FE_{100}C$) are used in different settings but the EBCTCG trial showed no significant difference in outcomes for regimens where only the anthracycline dose was increased.

4-Weekly CMF 6 cycles

Cyclophosphamide	500 mg/m² IV days 1+8
Methotrexate	40 mg/m² IV days 1+8
5-Fluorouracil	500 mg/m² IV days 1+8

3-Weekly AC or EC 4 cycles

Adriamycin	60 mg/m² IV day 1/epirubicin 90 mg /m² IV day 1
Cyclophosphamide	600 mg/m² IV day 1

4-Weekly CAF 6 cycles

Cyclophosphamide	100 mg/m² IV day 1
Adriamycin	30 mg/m² IV day 1
5-Fluorouracil	500 mg/m² IV day 1

4-Weekly CEF 6 cycles

Cyclophosphamide	75 mg/m² IV day 1
Epirubicin	90 mg/m² IV day 1
5-Fluorouracil	500 mg/m² IV day 1

Patients with node-positive disease have additional benefit when taxanes are added.

Docetaxel	75 mg/m² IV day 1, 3-weekly for 3 cycles

Neoadjuvant chemotherapy for patients with inoperable findings should have an anthracycline included if available. Including a taxane may even add further benefit. The following neoadjuvant regimen is suggested before surgery:

Adriamycin	60 mg/m² IV day 1, 3-weekly for 4 cycles
Cyclophosphamide	600 mg/m² IV day 1, 3-weekly for 4 cycles

In cases where taxanes are available this should be followed by:

Docetaxel   75 mg/m^2 IV day 1,
                        3-weekly for 4 cycles

Stage IV disease Endocrine therapy should always be considered first for a patient with stage IV disease (see Chapter 30).

In cases of resistance or high tumor load, a patient who has not been treated with chemotherapy before should receive an anthracycline as first-line therapy. Single-agent therapy is preferred. The number of cycles will depend on cumulative toxicity (see below) and effects on the tumor load. The therapy should be given as long as the benefit outweighs the side-effects. Weekly administration gives fewer side-effects, for example:

Epirubicin   30 mg/m^2 IV day 1

Common chemotherapeutic drugs used in gynecological cancers

Cisplatin

This is an alkylating agent. It is used in low doses as part of concurrent chemo-radiation in locally advanced cancer of the cervix. It is also used in higher doses as palliative chemotherapy in recurrent cancer of the cervix. In high doses it is a component of the BEP regime for germ cell tumors of the ovary as well as part of the EMA/EP regime for choriocarcinoma.

Cisplatin acts through inhibition of DNA precursors, inter- and intra-strand alkylation and non-specific cell cycle phase activity. Administration is intravenous. Cisplatin is cleared by the kidneys mainly by glomerular filtration. Normal renal function must be ensured before administration. The most common toxicities are nausea, vomiting and renal dysfunction. Vomiting may be acute or delayed. The renal toxicity can be decreased by ensuring rapid clearance of the drug by saline or mannitol diuresis. This has been described under the section on side-effects. Adequate hydration and urinary output must be maintained during the 24 h following infusion, maintaining a urinary output of at least 100 ml/h. Other toxicities are ototoxicity (irreversible) and peripheral sensory neuropathy.

Carboplatin

This is a platinum compound closely related to cisplatin. It has replaced cisplatin in many of the chemotherapy regimens (e.g. epithelial ovarian cancer) due to its improved toxicity profile, causing less nausea, vomiting, renal as well as neuro- and ototoxicity. Its main dose-limiting toxicity is hematological. Approximately 70% is excreted unchanged by glomerular filtration by the kidney. Carboplatin is dosed according to the patient's 24 h creatinine clearance as described under the section on ovarian cancer in this chapter.

5-Fluorouracil

5-Fluorouracil is an anti-metabolite. It blocks thymidine synthesis and thus DNA replication. It is usually used intravenously but can also be applied topically. Its main side-effects are myelosuppression and gastrointestinal side-effects. Topical application can cause dermatitis. 5-Fluorouracil is only stable in the presence of folinic acid and should be given together with leucovorin (however, through different lines, as they don't mix). Oral folinic acid may be used if leucovorin is not available but it is less efficacious.

Paclitaxel, docetaxel

Paclitaxel is metabolized in the kidney and biliary excretion is important. Acute hypersensitivity was the most important side-effect, but the incidence is greatly reduced by adequate pre-mediation with dexamethasone and anti-histamines and H1 and H2 blockers. Neutropenia is the main dose-limiting toxicity. The nadir occurs 8–11 days after administration and recovery occurs within 20 days. Other side-effects are alopecia, peripheral neurotoxicity (mainly neurosensory), peri-treatment myalgia which responds to simple analgesics, asymptomatic bradycardia, mucositis and inflammation at the injection site. Nausea and vomiting are uncommon.

Methotrexate

This is a folate antagonist and acts by binding to dihydrofolate reductase. Cellular protein synthesis, DNA and RNA production and cellular replication is affected. Leucovorin rescue is used 24 h after administration of methotrexate to reduce the toxic effects of methotrexate. The drug is mostly excreted by the kidney with a small amount through bile. Decreased renal function can result in toxicity. Patients must be adequately hydrated and urine alkalinized to reduce renal side-effects.

Myelosuppression occurs at about 7–10 days post-administration. Vomiting, diarrhea, stomatitis and mucositis can occur. Other side-effects are pulmonary, dermatologic and hepatic.

Cyclophosphamide

It is an alkylating agent and is largely metabolized in the liver into active compounds. It is excreted in the urine. Myelosuppression occurs 8–14 days after administration. Nausea and vomiting can be delayed, occurring 6–8 h after administration, so anti-emetic prophylaxis should be given for 24 h. Alopecia, skin and nail changes, increased liver enzymes and rarely jaundice can occur. Hemorrhagic cystitis (adequate hydration decreases the incidence) and secondary leukemia are other side-effects described.

Ifosfamide

This is an alkylating agent and is activated in the liver and excreted in the urine. Myelosuppression occurs 7–10 days after administration. Renal toxicity and hemorrhagic cystitis is common and mesna (an organosulfur compound) must be used as a continuous infusion of 4.5 g/m²/day and the patient must be adequately hydrated. Alopecia, skin and nail changes, increased liver enzymes may occur. Neurological toxicities may manifest with, lethargy, confusion, somnolence, disorientation, malaise and even coma.

Actinomycin D

This is an anti-tumor antibiotic and acts by inhibiting DNA transcription and RNA translation. It is excreted through the urine and bile. Myelosuppression occurs 10–14 days after administration. Nausea and vomiting starts 1 h after administration and can last for several hours. Mucositis, stomatitis, diarrhea, alopecia, erythema and skin changes can occur. Extravasation can cause tissue necrosis. Severe skin sensitivity can occur in previously irradiated tissue (radiation recall).

Bleomycin

This is an anti-tumor antibiotic and causes DNA single-strand breaks as well as DNA degradation. It is excreted through the kidney by glomerular filtration. Myelosuppression, nausea and vomiting is mild. Bleomycin can cause hyperpigmentation in skin folds and creases, alopecia, anaphylactic reactions and fever. The most serious toxicity is interstitial pneumonitis and lung fibrosis.

Doxorubicin, Adriamycin, epirubicin

These are anti-tumor antibiotics and their anti-cancer actions are by topoisomerase II inhibition, DNA intercalation and free radical formation. Anthracyclines are the major cornerstones of chemotherapy treatment in breast cancer. Doxorubicin is used together with ifosfamide in one of the regimens for the treatment of uterine sarcoma. It is metabolized in the liver. Most of the drug after metabolism is excreted in the bile with smaller amounts in the urine. Dose reductions are recommended for hyperbilirubinemia (1.2–3 mg serum bilirubin/100 ml, 50% of normal dose; >3 mg/100 ml serum bilirubin, 25% of normal dose). Toxicities include myelosuppression, nausea, vomiting, mucositis and stomatitis, alopecia, red or pink-colored urine and hyperpigmentation. Extravasation results in skin necrosis. Post chemotherapy anti-emetic prophylaxis should be given for 48 h.

Cardiomyopathy is a particular side-effect of these drugs. The incidence of cardiomyopathy is related to the cumulative dose of the drugs. A maximum of dose of 900 mg/m² epirubicin (3.3% congestive heart failure) and a maximum of dose of 550 mg/m² Adriamycin must not be exceeded in a patient's lifetime! Always look for new shortness of breath or tachycardia in patients on anthracyclines and do not start the drug if the patient already complains about such symptoms.

Pre-existing cardiac disease as well as prior mediastinal radiation may increase the incidence of cardiac toxicity. An echocardiogram should be performed prior to chemotherapy to confirm normal cardiac function if facilities for this examination exist.

Vinblastine and vincristine

These are plant-derived anti-mitotic agents and act by inhibiting microtubule assembly. They are mainly metabolized by the liver and excreted in the bile. Potential side-effects are myelosuppression, abdominal cramps, alopecia, peripheral neuropathy (dose limiting) and autonomic neuropathy. These drugs can cause constipation, so laxatives should be prescribed, Anaphylactic reactions, joint pains especially the temporo-mandibular joint and SIADH (syndrome of inappropriate antidiuretic

hormone secretion) can occur. Extravasation can cause pain and necrosis. In addition, vincristine can cause mild liver enzyme elevations and very rarely cortical blindness.

Etoposide

Etoposide can be given orally or IV. It is well absorbed through the gastrointestinal tract and is mainly excreted in the urine unmetabolized. About 10–15% is eliminated in the bile and passes in the feces. The main dose-limiting side-effects are myelosuppression with the nadir at 7–14 days and recovery by 20 days. Nausea and vomiting are common after oral administration. Alopecia, anaphylaxis, and peripheral neuropathy are other potential side-effects.

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