Chapter 23
General Principles of Cancer Chemotherapy

Chemotherapy is an extremely important component of childhood cancer treatment. It has dramatically transformed the prognosis of most malignant childhood tumors, which are usually chemotherapy-sensitive. The relative tolerance of children to chemotherapy compared with adults also contributes to good patient outcomes. In addition, modern chemotherapy includes new agents which selectively target tumor cells, thus limiting toxicity.

Prior to initiating a chemotherapy protocol, a definitive diagnosis should be established and a printed pathology/hematology report should preferably be available. Adequate information must be provided to the patient and/or the parents about the disease, its treatment and treatment-related complications. Chemotherapy should then be initiated by a specialized medical team according to a specific treatment protocol. While receiving chemotherapy, the patient should be seen regularly to assess treatment response, as well as to monitor for immediate and late treatment-related toxicity after completion of treatment.

Tumor Growth and Sensitivity to Chemotherapy

Chemotherapy drugs have an anti-mitotic action which is more pronounced in cells that have a high rate of cell division. The rate of tumor growth varies from one tumor to another, but also in different parts of the same tumor. This is mainly due to genetic, but also external and internal variables in the particular microenvironment.

Various models explaining tumor growth have been proposed. According to the Gompertzien model, growth takes place through an initial slow phase, followed by exponential proliferation and then a significant decrease in proliferation once the tumor mass reaches a critical volume. Growth is thus based on a sigmoid curve. The slowdown is explained by the mismatch between availability of metabolic building blocks and the metabolic needs of tumor cells, leading to anoxia and tumor necrosis.

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A significant fraction of tumor cells will then enter the quiescent cell phase (G0) and become insensitive to chemotherapy. This type of resistance is termed the kinetic type.

The proliferation of tumor cells may also be affected by genetic mutations, which lead to cellular resistance (the genetic type of resistance) with selection of a cell clone with a proliferative advantage. Metastatic lesions, which occur after multiple cell divisions, as well as large tumors are also more likely to be more resistant to chemotherapy. According to the mathematical model of Goldie and Coldman, when a tumor is detected, it already contains resistant clones, of which the magnitude depends on the frequency of genetic mutations and of the tumor mass.

Other mechanisms of tumor resistance to chemotherapy include modification of the chemotherapy receptor and metabolic inactivation or excretion of the active molecule of the drug. The tumor cell may also be able to repair chemotherapy-induced damage.

Chemotherapy resistance may occur to several different agents simultaneously. The acquisition of this multi-drug resistance (MDR) is due to the expression of p-glycoprotein and/or multi-drug resistance-associated protein on the tumor cell membrane. The presence of these two proteins is associated with a poor treatment response and prognosis.

Chemotherapy Mechanisms of Action

The induction of apoptosis is one of the predominant mechanisms of action. Apoptosis is a physiological cell death in which the cell condenses and fragments without altering surrounding tissues and without causing an inflammatory reaction. The cell cycle is divided into four phases (Fig. 23.1). The critical check points at which the cell has to either undergo DNA repair and continue the process of division or activate apoptosis, lie between phases G1 and S and phases G2 and M. At these critical points, the cell requires the interaction of cyclins and enzymes called cyclin-dependent kinases to regulate these processes.

Anti-mitotic drugs may be phase independent or have an effect only in certain phases of the cell cycle. For example, cytarabine is phase S-dependent, while

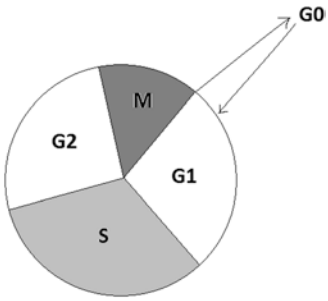

Fig. 23.1 Cell cycle. Phase S (DNA synthesis), phase M (mitosis), and phases G1 and G2 (Gap). Cells that are not in this mitotic cycle are in phase G0 (rest phase)

Table 23.1 Classification of the major chemotherapy agents used for childhood cancer

Alkylating agents	*Chemotherapy agents*
Nitrogen mustards	Chlorambucil, chlormethine, cyclophosphamide, ifosfamide, melphalan
Hydrazines and triazines	Procarbazine, dacarbazine, temozolomide
Nitrosureas	Carmustine, lomustine
Metal salts	Carboplatin, cisplatin
Alkylsulfonates	Busulfan
Antimetabolites	
Folate antagonists	Methotrexate
Purine antagonists	Fludarabine, 6-mercaptopurine, 6-thioguanine
Pyrimidine antagonists	5-Fluorouracil, cytarabine, gemcitabine
Topoisomerase inhibitors	
Camptothecin derivatives	Topotecan, irinotecan
Epipodophyllotoxins	Etoposide, teniposide
Other	Bleomycin
Anthracyclines	Daunorubicin, doxorubicin (synonym adriamycin), epirubicin, idarubicin.
Spindle poisons	
Vinca-alkaloids	Vincristine, vinblastine, vindesine, vinorelbine
Other	Paclitaxel
Other	
Asparaginase, Tretinoin (ATRA)	

vincristine only affects cells in phase M. Depending on their mechanism of action, the chemotherapy drugs are classified into four major groups: the alkylating agents, topoisomerase inhibitors, the antimetabolites, and the plant alkaloids (Table 23.1).

Alkylating agents are drugs that have the property to transfer an alkyl group to proteins that bind together to form the double helix DNA structure. DNA synthesis is impaired due to this alkylation process, but the alkylating agents are active in all phases of the cell cycle. They are important in the treatment of slow-growing cancers, but are also used widely in the treatment of leukemia, lymphoma, sarcoma, neuroblastoma, nephroblastoma, retinoblastoma, osteosarcoma, Ewing sarcoma, germ cell tumors, and brain tumors.

Antimetabolites also interfere with DNA synthesis and are S phase-dependent. Their activity is dependent on rapid cell proliferation. Some have a structural analogy with physiological molecules (folic acid, purine or pyrimidine antagonists), while others have an inhibitory effect on enzymes necessary for DNA synthesis.

Inhibitors of topoisomerases play a major role in the restructuring (coiling and uncoiling) of DNA for transcription, replication, and mitosis. Depending on their mechanism of action, these drugs are grouped into camptothecin derivatives inhibiting topoisomerase I (topotecan and irinotecan) and the epipodophyllotoxins (etoposide and teniposide) inhibiting topoisomerase II.

Anthracyclines are also known as antitumor antibiotics and were derived from the Streptomyces species. The mechanism of action occurs via multiple pathways,

Fig. 23.2 Anthracyclines most often have a characteristic *red*/*orange* color. Mitoxantrone has a blue color

such as impaired DNA synthesis, DNA intercalation, inhibition of topoisomerase I, induction of apoptosis, the generation of free radicals and an anti-angionetic action. These drugs are usually red or orange in color (Fig. 23.2). It is important to limit the cumulative dose of anthracyclines in order to reduce the risk of cardiotoxicity.

Spindle poisons bind to microtubules, which interfere with the formation of the tubules. They are phase M-dependent.

Recent developments: Research in the field of cancer drugs have different focus areas, e.g. reduction in toxicity, improving efficacy, and the development of novel agents. Liposomal anthracyclines have been developed in order to reduce the cardiotoxicity of this class of drugs. Asparaginase conjugated to polyethylene glycol (PEG-asparaginase) reduces immunogenicity and has a longer half-life. New classes of drugs specifically targeting tumor cells have emerged, e.g. rituximab, targeting tumor cells expressing CD20 on their surface, and many other monoclonal antibodies.

Most cancer drugs are metabolized by the liver and eliminated via urinary excretion. For this reason, it is essential to determine renal and hepatic function prior to starting treatment, as well as intermittently during treatment. In the case of renal or hepatic insufficiency, dosages should be adjusted. Drug interactions must also be

taken into account. For example, the use of anti-convulsants increases the catabolism of some chemotherapeutic agents.

First-line treatment protocols typically involve combination therapy, while monotherapy is sometimes used in metronomic or palliative therapy. The goal of combination therapy is to overcome drug resistance by targeting tumor cells in various ways.

Pharmacological Data

To understand and adapt chemotherapy treatment, it is important to know the behavior of each drug once it has been administered, e.g. bioavailability, distribution, biotransformation, and excretion. The bioavailability of drugs given by mouth may vary from one individual to another, as well as in the same individual at different points in time. Hepatic metabolism can significantly reduce the bioavailability of some drugs (e.g. 6-mercaptopurine). Several drugs are transported bound by albumin. A decrease in albumin will thus result in a high concentration of free drug and consequently more toxicity. Furthermore, third space dissemination (ascites, pleural effusion) is responsible for a decrease in drug clearance and greater toxicity. This is noted in particular when high-dose methotrexate is administered to patients with non-Hodgkin lymphoma. Drug clearance may also be reduced in the case of renal or hepatic failure (Table 23.2) and doses of certain drugs should be adjusted as indicated in Table 23.2.

Inherited or acquired impaired hepatic metabolism may cause major toxicity. In patients with a deficiency of thiopurine methyl transferase, an enzyme that degrades azathioprine and 6-mercaptopurine, these drugs are the cause of excessive toxicity at normal doses. Drugs metabolized by microsomal P450 in the liver have a reduced clearance when ketoconazole or anti-retroviral drugs are administered concomitantly and increased clearance in case of simultaneous treatment with anti-convulsants. Examples of such drugs include cyclophosphamide, the vinca-alkaloids, and the epipodophyllotoxins.

Table 23.2 Chemotherapy drugs that require dose adjustment in renal or hepatic failure

Renal failure	Liver disease
Bleomycin	Daunorubicin
Carboplatin	Doxorubicin
Cisplatin	Epirubicin
Cyclophosphamide	Idarubicin
Etoposide	Vincristine
Hydroxyurea	Vinblastine
Ifosfamide	Vinorelbine
Methotrexate	
Nitrosoureas	
Topotecan	

Administration of Chemotherapy

Chemotherapy is usually administered in timed cycles in order to allow normal tissues to regenerate in between cycles. Usually the more intensive the chemotherapy, the longer the time interval between treatment cycles. In more recent years, dose-dense chemotherapy protocols have been studied to determine whether outcome would be improved, for example giving chemotherapy cycles 2 weekly instead of every 3 weeks with supportive granulocyte colony stimulating factor. Several cycles are needed to eliminate the disease. The disappearance of clinical and radiological signs that signifies remission, does not equate to cure since continued chemotherapy is required in order to eradicate all undetectable tumor cells.

When protocols are designed, the method of administration and dose of a drug are also important factors to take into account. For example, methotrexate is given intravenously at high doses in order to achieve better central nervous system (CNS) penetration in the treatment of acute leukemia and is also given intrathecally to eradicate leukemic blasts in the cerebrospinal fluid and prevent CNS relapse.

The method of administration of chemotherapy drugs is varied according to what preparation of the drug is available. Chemotherapy regimens for leukemias and non-Hodgkin lymphomas include oral, intravenous, intramuscular, and intrathecal drugs. Hodgkin lymphoma and solid tumors are usually treated only with intravenous chemotherapy. Asparaginase may be given intravenously or intramuscularly, but the incidence of anaphylaxis is significantly reduced when given intramuscularly, thus most pediatric oncology units use the intramuscular route. Whenever asparaginase is being administered, a trolley should be prepared with the necessary drugs and equipment to treat anaphylaxis, if it should occur. The patient should also be observed for at least 1 hour. Glucocorticosteroids are equally effective whether it is given orally or intravenously. In some countries it may be difficult to obtain oral dexamethasone, thus the intravenous form may be used.

Chemotherapy should preferably only be administered in a pediatric oncology unit where staff have been trained to handle these drugs. After the required chemotherapy drugs have been prepared in a sterile manner in a laminar flow box by a trained pharmacist or other experienced healthcare worker, the drug name, dose, volume, method of administration, patient details, date prepared, and expiration time should be checked by two persons. The administration should take place as soon as possible, since some agents such as cyclophosphamide and dacarbazine expire rapidly. Most other agents are stable for 8 hours after preparation. Protection against light may be necessary for some agents, such as dacarbazine. The period of administration is very important, since toxicity may be increased by a longer infusion time (e.g. doxorubicin). Therefore, the treatment protocol should be followed meticulously regarding prescription and administration instructions. The information on the drug pamphlet should also be studied carefully.

It is extremely important to remember that only three drugs may ever be administered via the intrathecal route: methotrexate, cytarabine, and hydrocortisone (given to prevent chemical arachnoiditis). In some treatment protocols, vincristine

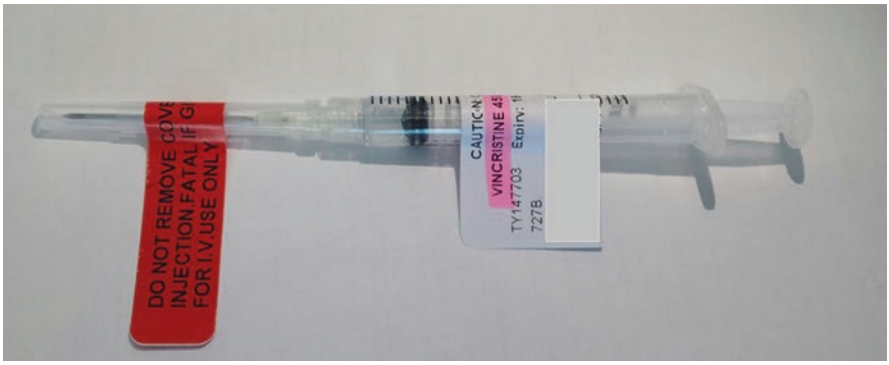

Fig. 23.3 Syringes with vincristine should be clearly marked with a bright colored sticker to prevent inadvertent intrathecal administration

and methotrexate are administered on the same day. The utmost care should be taken not to administer vincristine intrathecally, since that is invariably fatal. The vincristine should be kept separate in a different plastic bag or container and should be marked clearly with a bright colored sticker (Fig. 23.3).

Staff handling chemotherapy should be adequately trained in the correct handling of these drugs. Gloves not penetrable by chemotherapy should be worn. If chemotherapy-impenetrable gloves are not available, double latex gloves may be used. Tablets should not be crushed or manipulated in open areas. If a chemotherapy drug is spilled, it should be cleaned immediately. If it should come into contact with the skin or eyes, the affected area should be washed or rinsed immediately. Bodily secretions should be handled correctly and disposed of in the chemotherapy waste bin. Parents should also be taught how to handle oral chemotherapy and bodily secretions appropriately at home.

Some drugs require concomitant intravenous fluids (hyperhydration), such as cyclophosphamide, ifosfamide, intravenous methotrexate, high-dose cytarabine (≥ 1 g/m^2) and cisplatinum. Mesna is usually given together with ifosfamide (and sometimes cyclophosphamide) in order to prevent hemorrhagic cystitis. Leukovorin is given after a methotrexate infusion to supply substrate for folate production in order to rescue normal cells. Urine alkylinization when methotrexate is administered, is used to limit renal failure induced by methotrexate. Lubricating eye drops and piridoxine are given together with high-dose cytarabine to prevent toxicity.

A patient receiving an infusion of a chemotherapeutic drug, or who has received a drug intrathecally or intramuscularly, should be observed very carefully for signs of anaphylaxis, hypotension, fever, fluid overload, hematuria, nausea, and vomiting or any other side-effect. Most units provide conscious sedation for the administration of intrathecal chemotherapy, since children need to have this painful procedure multiple times. Each unit should thus have a protocol for the care of patients who receive sedation.

Venous Access

Secure venous access is very important, since cancer treatment lasts many months and sometimes even years. It needs to be ensured that intravenous chemotherapy may be administered intravenously without delays due to lack of venous access. An experienced member of the medical team should place the intravenous catheter and ensure that it is working well. If an intravenous bolus of potentially vesicant chemotherapy is administered, it is wise to connect a 50 millilitre bag of fluid and let the fluid run in at a fast rate so that it can be ensured that the venous catheter is not leaking. During injection, the site should be inspected for any redness, swelling and the patient should be asked to report any pain immediately. If a peripheral venous catheter is in situ for several days, it should be inspected often for any signs of thrombophlebitis or leaking.

For patients with poor venous access, it may be advisable to insert a central venous catheter (CVC). A jugular, subclavian or femoral central venous pressure (CVP) line may be inserted if short periods of venous access are needed or while the placement of a CVC is being awaited. Another short-stay option is a peripherally inserted central catheter (PICC) line. The most commonly used CVCs however, are Broviac lines and portocaths or ports. Broviac lines exit the chest wall anteriorly and thus breach the skin barrier. A port is completely submerged under the skin. For this reason, the risk of infection is lower with a port. Port needles are very expensive though and this may limit the use of ports in developing countries. All central catheters must be handled in a sterile manner.

Chemotherapy Toxicity

The medical team must know the side-effect profile of each chemotherapy agent very well in order to prevent, monitor, and recognize adverse events.

Bone marrow suppression is the main and most important side-effect; also the most common cause for delays in chemotherapy administration. The drugs most frequently causing myelosuppression in Pediatric oncology is shown in Table 23.3. The severity of myelosuppression is influenced by the dose of the chemotherapy agent, bone marrow reserve, intensity of the treatment protocol, and individual pharmacokinetics. The lowest peripheral blood counts are usually seen 7–10 days after administration of chemotherapy. Leukopenia, specifically neutropenia, predisposes the patient to infection with the highest risk for neutropenia below 0.5×10^9/L and extended periods of neutropenia. Granulocyte colony stimulating factor (GCSF) may be used in selected cases of febrile neutropenia or as part of some treatment protocols to prevent neutropenia and treatment delays. Anemia and thrombocytopenia may require supportive blood- and blood-product transfusions.

Nausea and vomiting are common if no preventative anti-emetic therapy is given. The mechanism of nausea and vomiting is stimulation of the serotonin (5-hydroxy-

Table 23.3 Chemotherapy drugs with a high potential of hematopoietic toxicity

Actinomycin D	Idarubicin
Cytarabine	Ifosfamide
Busulfan	Mercaptopurine
Carboplatin	Mitoxantrone
Cisplatin	Nitrosureas
Cyclophosphamide	Teniposide
Daunorubicin	Thioguanine
Doxorubicin	
Dacarbazine	
Etoposide	
Hydroxyurea	

Table 23.4 Emetogenic potential of chemotherapy agents used in treating childhood cancers (HD=high dose)

Level of emetogenic risk	Percentage of patients who experience nausea and vomiting (%)	Drugs
Level 4 (high)	>90	Cisplatin, HD cyclophosphamide, Dacarbazine, Dactinomycin
Level 3 (moderate)	30–90	Carboplatin, Cyclophosphamide, Daunorubicin, Doxorubicin, Idarubicin, Ifosfamide, HD Cytarabine (Ara C), Epirubicin, Irinotecan
Level 2 (Low)	10–30	Cytarabine, Etoposide, Gemcitabine, Methotrexate, Mitoxantrone, Paclitaxel, Topotecan
Level 1 (Minimal)	<10	Vinblastine, Vincristine, Vinorelbine, Fludarabine, Bleomycin, 2-Chlorodeoxyadenosine, Rituximab

tryptamine) receptors at the level of the vagal and splanchnic nerves. Inhibitors of these receptors, such as ondansetron and granisetron, are very effective anti-emetic agents. Table 23.4 lists chemotherapy drugs with varying emetogenicity.

Other common side-effects include temporary hair loss, mucositis (Table 23.5), diarrhea, constipation, and abdominal and bone pain. Other toxicities include renal, neurological (Table 23.6), hepatic, pulmonary (Table 23.7) and cardiac side-effects, as well as skin manifestations. The routes of elimination, some drug interactions, precautions and side-effects are summarized in Table 23.8.

Gonadal toxicity that may lead to infertility is observed especially with alkylating agents. It is dose-dependent and is more readily seen in boys.

Table 23.5 Chemotherapy drugs causing mucositis

Actinomycin D	Fluorouracil
Cytarabine	Idarubicin
Busulfan	Ifosfamide
Bleomycin	Methotrexate
Cyclophosphamide	Mercaptopurine
Daunorubicin	
Doxorubicin	Mitoxantrone
Epirubicin	Nitrosureas
Etoposide	Procarbazine
Etoposide	Thioguanine
Hydroxyurea	

Table 23.6 Chemotherapy drugs with a potential for neurological toxicity

Cytarabine	Nitrosureas
Asparaginase	Pentostatine
Carboplatin	Procarbazine
Cisplatin	Tretinoin
Fluorouracil	Vinblastine
Ifosfamide	Vincristine
Interferon	Vinorelbine
Methotrexate	

Table 23.7 Chemotherapy drugs with a potential for pulmonary toxicity

ATRA	Ifosfamide
Cytarabine	Mercaptopurine
Azathioprine	Methotrexate
Bleomycin	Melphalan
Busulfan	Nitrosureas
Cyclophosphamide	Procarbazine
Etoposide	Vincristine
	Vinblastine

Secondary cancers may occur following treatment with alkylating agents, epipodophyllotoxins and anthracyclines. The risk is higher in association with radiotherapy. Secondary cancers usually occur 5 years after treatment.

Summary

- Chemotherapy should be given according to a standard treatment protocol after a definitive diagnosis has been made.
- It must preferably be administered in a pediatric oncology unit by trained healthcare workers.
- The main mechanisms of action are interference in cell division and DNA synthesis, as well as induction of cell apoptosis.

Table 23.8 Main chemotherapy agents (drug pamphlets should still be consulted for complete information)

Drug	Mechanism of action/metabolism	Major side-effects	Precautions/Drug Interactions
Alkylating agents			
Cyclophosphamide	Activation in the liver by oxidative microsomal P450; metabolites include acrolein which causes bladder toxicity. Urinary excretion	Myelosuppression Hemorrhagic cystitis Headache Nausea/vomiting Alopecia Stomatitis Sterility More rarely: Inappropriate ADH (SIADH) Secondary cancer	Prevention of cystitis by good diuresis. At high doses: preventative administration of Mesna Phenobarbital, phenytoin, and other drugs that stimulate hepatic P450 may increase toxicity. Digoxin levels are reduced by cyclophosphamide
Dacarbazine (DTIC)	Activation in the liver by oxidative microsomal P450. Especially urinary elimination Action not phase-dependent	Myelosuppression, Nausea/vomiting Pain at injection site Alopecia, photosensitivity Rarely: Diarrhea, stomatitis, thrombosis, anaphylaxis	Phenobarbital, phenytoin, and other drugs that stimulate hepatic P450 reduces the effectiveness of dacarbazine
Ifosfamide	Activation in the liver by oxidative microsomal P450; metabolites include acrolein (bladder toxicity) and chloroacetaldehyde (neurological toxicity). Urinary excretion	Myelosuppression, hemorrhagic cystitis Neurotoxicity: dizziness, confusion, ataxia, lethargy and rarely coma nausea/vomiting, alopecia Stomatitis Urticaria, Hyperpigmentation, Renal tubular acidosis, SIADH	Cystitis: Prevent by hyperhydration and Mesna Phenobarbital and phenytoin increase toxic metabolites. Cimetidine and allopurinol increases the toxicity of ifosfamide
Nitrosureas	Effect is cycle-independent Fat-soluble molecules with good brain penetration	Myelosuppression, Nausea/vomiting Stomatitis, esophagitis, alopecia, interstitial lung disease Dizziness, ataxia	Cimetidine reduces the degradation of the nitrosureas
Procarbazine	Activation in the liver by oxidative microsomal P450. Hepatic degradation and urinary elimination	Myelosuppression, nausea/vomiting, flu-like symptoms, Hypersensitivity, hyperpigmentation Rarely neuropsychiatric disorders, photophobia, papilledema	Hypertension, Fever, convulsion if association with tricyclic antidepressants

(continued)

Table 23.8 (continued)

Drug	Mechanism of action/metabolism	Major side-effects	Precautions/Drug Interactions
Cisplatinum	Long plasma half-life (close to 3 days) and remain several months in tissues. Mainly urinary excretion	Renal toxicity Peripheral neuropathy Ototoxicity Nausea/vomiting Hypokalemia, hypomagnesemia	Hyperhydration Monitoring of creatinine, electrolytes (magnesium, calcium) Inhibits the elimination of bleomycin, etoposide, methotrexate, and ifosfamide Other nephrotoxic agents (e.g., amikacin) increase the risk of nephrotoxicity
Carboplatin	Half-life 2–3 hours Urinary excretion	Myelosuppression Nausea/vomiting Peripheral neuropathy, Ototoxicity Hypersensitivity reaction	Adjust dose according to creatinine clearance: Creat clearance ≥60 mL/min: dose = 360 mg/m^2 Creat Clearance 41–59 mL/min: Dose = 250 mg/m^2 Creat clearance ≥16–40 mL/min: dose = 200 mg/m^2
Antimetabolites			
Cytosine arabinoside (Ara C)	Urinary excretion	Myelosuppression Nausea/vomiting Mucositis, diarrhea, Arachnoiditis (intrathecal injection) Neurotoxicity (lethargy, confusion, ataxia) Conjunctivitis AraC syndrome: fever, myalgia, flu-like symptoms, bone pain, and maculopapular rash	Prevention of conjunctivitis by eye drops (for high-dose AraC) Hyperhydration for high dose AraC Higher risk of pancreatitis in association with L-asparaginase Toxicity increases if association with cisplatinum, hydroxyurea, and methotrexate Causes reduced effectiveness of gentamycin and digoxin

(continued)

Table 23.8 (continued)

Drug	Mechanism of action/metabolism	Major side-effects	Precautions/Drug Interactions
5-Fluorouracil	Half-life 10–20 min, mainly hepatic degradation	Myelosuppression, mucositis, diarrhea. Conjunctival irritation, photosensitivity, pigmentation of the infusion site veins, neurological disorders	Toxicity is increased if given together with leucovorin, methotrexate, trimetrexate Allopurinol inhibits the activation of the fluorouracyl and reduces its effectiveness
Hydroxyurea	Crosses the blood–brain barrier Short half-life Urinary elimination	Myelosuppression, Sometimes nausea and vomiting, mucositis, diarrhea Skin rash, erythema, Hyperpigmentation Alopecia	
6-Mercaptopurine (6MP)	6 MP is slowly degraded in the liver, mainly by xanthine oxidase	Myelosuppression Anorexia, nausea, vomiting, reversible cholestasis, photosensitivity	Allopurinol (xanthine oxidase inhibitor) may cause increased toxicity
Methotrexate (MTX)	Elimination is mainly urinary The half-life is 8–10 hours Significantly slower elimination in the case of effusion, leading to greater toxicity	Myelosuppression, stomatitis, renal failure At high dose: nausea, vomiting, renal tubular necrosis Acute encephalopathy, chronic leucoencephalopathy Intrathecal: aseptic meningitis, myelopathy, and encephalopathy	Folinic acid is an inhibitor of MTX. It is routinely given together with alkaline hyperhydration to reduce the toxicity of high-dose MTX Drugs carried by albumin (sulfonamides, aspirin, etc.) increase the free form of MTX and its toxicity L-Asparaginase and thymidine inhibit the activity of MTX Nonsteroidal anti-inflammatory drugs, penicillin, cephalosporins, phenytoin, and probenecid decreased renal excretion of MTX and increase the toxicity Trimethoprim is also an inhibitor of dihydrofolate reductase and may also increase the risk of toxicity. Should thus be avoided in the week of MTX administration

(continued)

Table 23.8 (continued)

Drug	Mechanism of action/metabolism	Major side-effects	Precautions/Drug Interactions
6-Thioguanine (6TG)	6-TG is degraded in the liver regardless of xanthine oxidase	Myelosuppression Stomatitis, diarrhea Nausea/vomiting Sinusoidal obstruction syndrome	
Anti-mitotic antibiotic			
Actinomycin D	Relative long half-life Biliary and urinary excretion	Myelosuppression Nausea/vomiting Alopecia Acne Hyperpigmentation Mucositis Rarely: hepatitis, anaphylaxis	
Bleomycin	Urinary excretion	Lung disease that can lead to fibrosis, especially in association with radiotherapy Hypersensitivity: fever, chills, pruritus, urticaria Hyperpigmentation and skin lesions Anorexia, mucositis	Phenothiazines increase the toxicity of bleomycin by competition at the level of the microsomal P450 Radiation therapy and oxygen increase pulmonary toxicity
Anthracyclines (Daunorubicin, doxorubicin, Idarubicin, Epirubicin, Mitoxantrone)	Quickly metabolized by the liver Also biliary excretion Some chromogenic derivatives are eliminated by the kidney sometimes giving a reddish color to the urine	Myelosuppression Congestive cardiomyopathy related to the formation of free radicals Cardiotoxicity is cumulative dose-dependent Mitoxantrone is less cardiotoxic Alopecia Nausea/vomiting	Cardioprotection by dexrazoxan may be considered when higher cumulative doses are used. Monitor left ventricular ejection fraction 6-MP increases the risk of hepatotoxicity

(continued)

Table 23.8 (continued)

Drug	Mechanism of action/metabolism	Major side-effects	Precautions/Drug Interactions
Spindle poisons			
Vinblastine, Vincristine, Vindesine, Vinorelbine	Vinorelbine is a semisynthetic derivative of vinblastine Activation in the liver by oxidative microsomal P450 Hepatic degradation and essentially biliary excretion	More frequent and more severe neurological toxicity with vincristine: Hypoesthesia, paresthesia, areflexia, mandibular pain, constipation that can evolve into paralytic ileus, optic atrophy, convulsion Moderate leukopenia especially with vinorelbine Rarely: nausea, vomiting, SIADH	Phenobarbital, calcium channel blockers, cimetidine, metoclopramide and drugs inhibiting P450 liver increase the production of metabolites. Vincristine reduces the level of phenytoin and digoxin. Filgastrim, administered concomitantly increase the risk of neuropathy L-asparaginase reduces the clearance of vincristine and must be administered 12–24 hours after vincristine
Inhibitors of topoisomerases			
Etoposide (VP16) Teniposide (VM26)	It is carried by albumin and may have greater toxicity in the case of hypoalbuminemia Hepatic metabolism and urinary excretion	Myelosuppression Nausea/vomiting Alopecia	Intravenous infusion must be given over an hour to avoid hypotension Concomitant administration of calcium channel blockers or methotrexate increases the toxicity of VP16
Topotecan	Topotecan undergoes activation in the plasma Urinary elimination	Myelosuppression Nausea/vomiting Alopecia Arthralgia Abdominal pain, microscopic hematuria	

(continued)

Table 23.8 (continued)

Drug	Mechanism of action/metabolism	Major side-effects	Precautions/Drug Interactions
Other agents			
L-asparaginase	Enzyme extracted from Escherichia coli or Erwinia chrysanthemi Short half-life No liver metabolism or renal elimination	Allergic reactions (chills, skin rash, urticaria, fever, laryngeal spasm, anaphylactic shock) usually occurring within 1 hour following administration More common in the case of intravenous injection Neurological disorder (cerebral thrombosis) Disorders of hemostasis (Deficiency of antithrombin, protein C and S) Nausea/vomiting Pancreatitis Hepatitis	In case of allergy it is recommended to use Asparaginase extracted from Erwinia chrysanthemi L ' Asparaginase blocks the action of methotrexate L-asparaginase reduces the clearance of vincristine and must be administered 12–24 hours after
All-trans retinoic acid (ATRA)	Indicated in acute promyelocytic leukemia Induces differentiation of promyelocytes into normal myelocytes Metabolism at the level of the hepatic P450 system Urinary and digestive elimination	ATRA syndrome: Leukocytosis, dyspnea, fever, pulmonary infiltrates, weight gain, pleurisy, pericarditis Toxicity of vitamin A: fever, headache, dryness mucocutaneous, cutaneous rash, conjunctivitis. Hypercholesterolemia	In case of ATRA syndrome: corticosteroids Drug interactions with drugs inhibiting or stimulating the hepatic cytochrome P450 system
Imatinib Dasatinib	Hepatic metabolism and eliminated primarily in the stool	Myelosuppression Nausea/vomiting Water retention: peri-orbital edema, pleurisy	Plasma levels changed by drugs affecting hepatic CYP3A4 (cyclosporine, ketoconazole, itraconazole)

- Depending on their mechanism of action, the main classes of agents are the alkylating agents, antimetabolites, topoisomerase inhibitors, anthracyclines, spindle poisons, and other.
- Chemotherapy agents are highly toxic and should be handled with care by medical staff who has taken the necessary precautions when handling these drugs.
- Measures to prevent or limit toxicity include hyperhydration, urine alkalinization, and the administration of leukovorin, mesna, lubricating eye drops and pyridoxine.
- Patients should be monitored carefully for acute and long-term side-effects.
- The main acute side-effects are myelosuppression, nausea and vomiting, mucositis, diarrhea, constipation, abdominal and bone pain and temporary hair loss.
- Long-term toxicity is to be taken into consideration and include infertility and the risk of a second cancer.
- Newer chemotherapy drugs have less toxicity, since they specifically target tumor cells.

Suggested Reading

Adamson PC, Bagatelli R, Balis FM, Blaney SM (2014) General principles of chemotherapy. In: Pizzo PA, Poplack GD (eds) Principles and practices of paediatric oncology, 6th edn. Lippincott Williams & Wilkins, Philadelphia, pp 279–355

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Safe handling of hazardous chemotherapy drugs in limited-resource settings (2013). A WHO and PAHO publication. www.paho.org

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