Cytotoxic Drugs

63

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Abstract

Cytotoxic drugs were the first class of drugs used to effectively treat neoplasms. Nitrosourea was the first drug developed. These drugs target DNA or metabolic steps which are crucial for cell division, thus leading to apoptosis (cytotoxic). They are broadly classified as alkylating agents, antimetabolites, natural products, and miscellaneous drugs. Alkylating agents cause interstrand linking of DNA through alkylation. Platinum compounds also cause inter- and intra-strand linkage but by forming DNA adducts. Antimetabolites act by inhibiting purine, pyrimidine, or both syntheses. Natural products include microtubule-damaging drugs like vinca alkaloids and taxanes; camptothecins and epipodophyllotoxins—which act by interfering with topoisomerase function; and anti-tumour antibiotics—which cause breaks in DNA strands. Miscellaneous group includes drugs with an entirely different mechanism, for example, tretinoin (ATRA) and arsenic trioxide (ATO) induce cell differentiation. There are many newer analogues in each class of drugs. The essential pharmacokinetic parameters and important indications which help to differentiate between these analogues are presented in the chapter. Though cytotoxic chemotherapy has offered hope to patients, the use of these drugs is accompanied by a number of adverse drug reactions (ADRs) mainly due to their action on normal rapidly dividing cells of our body. Currently targeted chemotherapy has gained importance in research due to their lesser incidence of ADRs.

Keywords

Cytotoxic · Chemotherapy · Anticancer · Antineoplastic

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63.1 Introduction

Cytotoxic drugs belong to the group of anticancer drugs which drive the cell into apoptosis, causing arrest in tumour progression. Hence, they target the DNA or metabolic pathways which are important for cell replication. Also, these targets should be unique in malignant cells or else it will result in toxicity due to attacks on the normal cell pathways. Nitrosourea was the first anticancer drug developed in 1898.

The U.S. army had played an important role in the development of nitrogen mustards (mechlorethamine). They derived it from the mustard gases used in the First World War. Studies of Goodman and Gilman in mouse lymphoma and clinical studies started the era of modern chemotherapy.

63.2 Classification and Mechanism of Action

Cytotoxic drugs can broadly be classified as below:

- Alkylating agents and platinum compounds
- Antimetabolites
- Natural products
- Miscellaneous

63.2.1 Alkylating Agents

The classification of alkylating agents is given in Box 63.1.

Box 63.1 Classification of Alkylating Agents

Alkylating agents	
Nitrogen mustards	Mechlorethamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, bendamustine
Ethyleneimines	Altretamine (hexamethylmelamine), thiotepa
Alkyl sulfonates	Busulfan
Nitrosoureas	Carmustine (BCNU), lomustine, streptozocin
Triazenes	Dacarbazine (DTIC), temozolomide
Methylhydrazines	Procarbazine
Platinum compounds[a]	Cisplatin, carboplatin, oxaliplatin

[a]Mechanism does not involve alkylation of DNA

Although platinum complexes are not true alkylating agents, they are discussed with this group because of the similarities in its mechanism of action and resistance with alkylating agents.

Mechanism of action of alkylating agents:

- Form reactive carbonium intermediates which covalently link to sites of high electron density (alkylation).
- Bifunctional alkylating agents mostly bind to N_7 atom of guanine (key target).
- Cross-linking of two nucleic acid chain occurs (interstrand linking).
- This results in cytotoxic and mutagenic effects in the cell.

Mechanism of action of platinum compounds:

- Form covalent metal adducts with DNA rather than alkylation like with alkylating agents; results in inter- and intra-strand linking.
- Enter cell through Cu transporter CTR1 and extruded via ATB7A/B and MRP1 transporters.
- Aquation occurs in cell resulting in the development of positive charge which reacts with nucleophilic sites in DNA.
- Low chloride favours aquation in cell and urine—hence, Cl diuresis prevents nephrotoxicity.
- Cytotoxicity depends on the intact mismatch repair (MMR) system which leads to single and double strand breaks.
- Oxaliplatin however does not depend on MMR system; hence, it shows better activity in colorectal cancer. It shows less dependence on high mobility group box (HMG) proteins unlike other platinum compounds, so forms fewer DNA adducts (lesser side effects).

63.2.2 Antimetabolites

The classification of antimetabolites is given in Box 63.2.

Box 63.2 Classification of Antimetabolites

Antimetabolites	
Folic acid analogues/ antagonists	Methotrexate, pemetrexed, pralatrexate, raltitrexed, lometrexol
Pyrimidine analogues	5-fluorouracil, capecitabine, floxuridine, trifluridine
Cytidine analogues	Cytarabine, azacitidine, gemcitabine
Purine analogues	6-thiopurine analogues (6-mercaptopurine, 6-thioguanine), cladribine, pentostatin, clofarabine, nelarabine, fludarabine

63.2.2.1 Mechanism of Action

Folate Analogues/Antagonists

- Drugs like methotrexate are structural analogue of folic acid and block dihydrofolate reductase (DHFR) and thus preventing the activation of folic acid.
- The active form is involved in carbon transfer reactions required for purine and pyrimidine synthesis. In the cell, methotrexate undergoes addition of polyglutamates; this form has additional inhibitory action and inhibits thymidylate synthase and other two enzymes in purine synthesis pathway (Fig. 63.1).

Pyrimidine Analogues

5-Fluorouracil (5-FU) gets converted to fluorodeoxyuridine monophosphate (FdUMP), which inhibits thymidylate synthase by competing with deoxyuridine

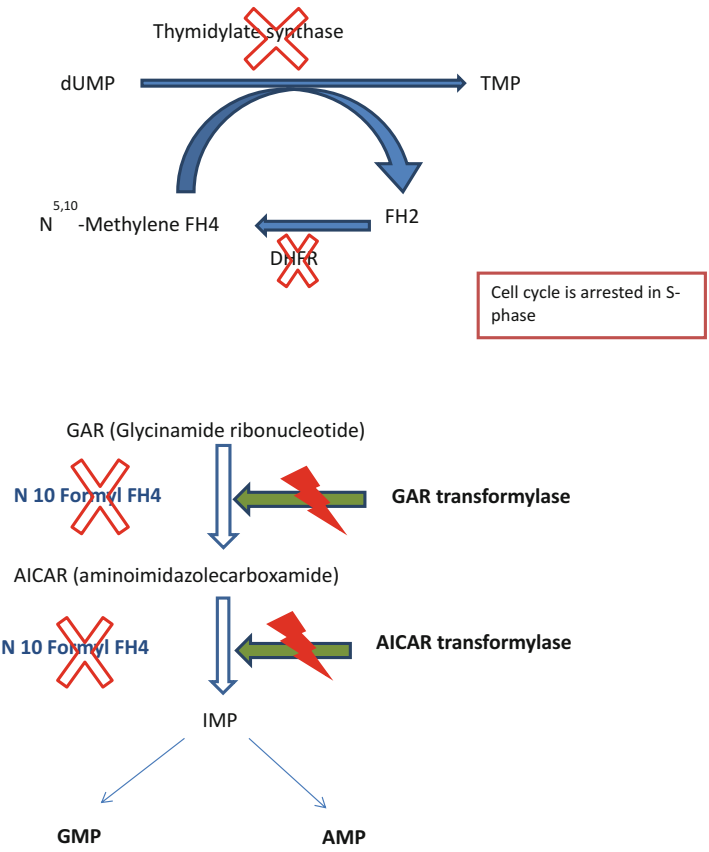

Fig. 63.1 Mechanism of action of methotrexate. *dUMP* deoxyuridine monophosphate, *dTMP* deoxythymidine monophosphate, *FH4* tetrahydrofolic acid, FH2 *dihydrofolic acid*, *DHFR* dihydrofolate reductase, *IMP* inosine monophosphate, *GMP* guanosine monophosphate, *AMP* adenosine monophosphate

monophosphate, thus inhibiting DNA synthesis. In addition 5-FU converts to fluorouridine triphosphate (FUTP) and gets incorporated into RNA (Fig. 63.2).

Cytidine Analogues

- Cytarabine—Drug enters via ENT1 and phosphorylation phosphorylates to arabinosylcytosine triphosphate (Ara-CTP). It competes with deoxycytidine triphosphate (dCTP) for incorporation into DNA and inhibits DNA polymerase in replication and repair.
- Azacitidine—It covalently binds to DNA methyltransferases and causes global demethylation leading to differentiation and apoptosis.
- Gemcitabine—In addition to ENT1, it uses CNT1 and a nucleobase transporter and has cytotoxic activity which is not confined to S phase.

Purine Analogues

6-Thioguanine (6TG) and 6-mercaptopurine (6MP) inhibit conversion of IMP to adenine and guanine nucleotides as well as inhibit the de novo pathway. 6-TG nucleotide gets incorporated into DNA and induces strand breaks and base mispairing (Fig. 63.3).

- Fludarabine—The active triphosphate inhibits RNA processing in addition to DNA.
- Cladribine—It produces DNA strand breaks and inhibits RNR (ribonucleotide diphosphate reductase). This drug is cytotoxic even if the cell is not in active division.
- Clofarabine is a newer congener that has better stability and uptake.
- Nelarabine—It is the only guanine nucleotide. Action is similar to other purine analogues.
- Pentostatin—It acts by inhibiting adenosine deaminase (ADA). This causes accumulation of intracellular adenosine and deoxyadenosine nucleotides which in turn block DNA synthesis.

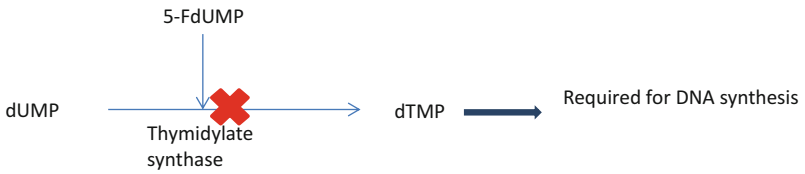

Fig. 63.2 Mechanism of action of pyrimidine analogues. *FdUMP* fluorodeoxyuridine monophosphate, *dUMP* deoxyuridine monophosphate, *dTMP* deoxythymidine monophosphate

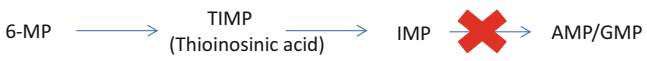

Fig. 63.3 Mechanism of action of purine analogues. *6-MP* 6-mercaptopurine, *TIMP* thioinosinic acid, *IMP* inosine monophosphate, *AMP/GMP* adenosine/guanosine monophosphate

63.2.3 Natural Products and Miscellaneous Drugs

The classification of natural products and miscellaneous drugs is given in Box 63.3.

Box 63.3 Classification of Natural Products and Miscellaneous Drugs

Natural products		
Microtubule-damaging agents	Vinca alkaloids	Vincristine, vinblastine, vinorelbine
	Eribulin	
	Taxanes	Paclitaxel, docetaxel
	Estramustine	
	Epothilones	
Camptothecin analogues	Topotecan, irinotecan	
Epipodophyllotoxins	Etoposide, teniposide	
Anticancer antibiotics	Dactinomycin, anthracyclines (doxorubicin, daunorubicin, idarubicin, mitoxantrone, epirubicin, valrubicin), mitomycin, bleomycin	
Miscellaneous	L-asparaginase, mitotane, trabectedin, hydroxyurea, retinoids, arsenic trioxide	

63.2.3.1 Mechanism of Action

Microtubule-Damaging Agents

- *Vinca alkaloids*
  Cell-cycle specific (CCS) agents similar to taxanes and epothilones block cell in mitosis. They bind specifically to β tubulin and block its polymerisation with alpha-tubulin. Thus, the mitotic spindle does not form and the cell gets arrested in metaphase. Eribulin also binds to same site and prevents microtubule assembly. Estramustine binds to beta-tubulin and prevents disassembly (Fig. 63.4).
- *Taxanes* bind to a different site on beta-tubulin and inhibit microtubule disassembly and hence, cell cycle is arrested in mitosis.
- *Epothilones*
  Bind to a distinct site on beta-tubulin and cause microtubule nucleation at different sites (dysfunctional stabilisation) which causes cell cycle arrest at G2-M interface.

Camptothecin Analogues

These are S phase specific. Inhibit topoisomerase 1 and inhibit the re-ligation step, thus causing accumulation of single stranded breaks. Collision of DNA replication fork with cleaved strand leads to double strand breaks (Fig. 63.5).

Epipodophyllotoxins

These drugs make ternary complexes with topoisomerase II and DNA, hence preventing resealing of the break. S and G2 phase are the most sensitive phases (Fig. 63.5).

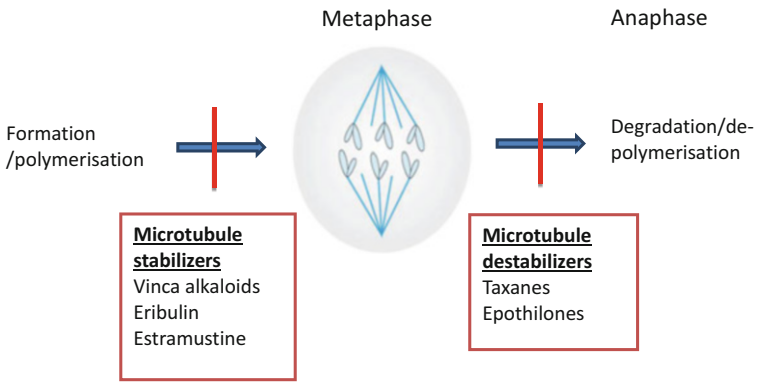

Fig. 63.4 Drugs acting on microtubules

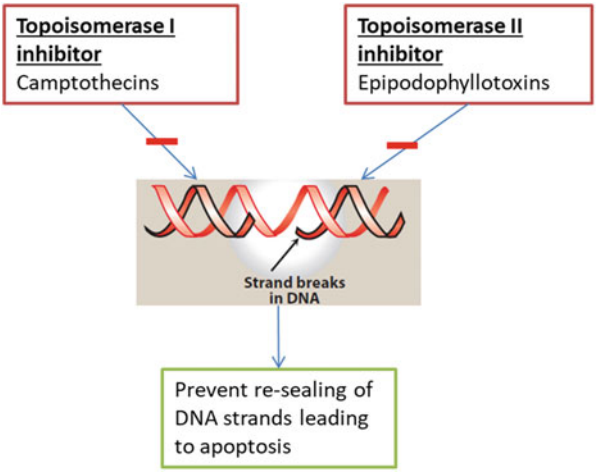

Fig. 63.5 Drugs inhibiting topoisomerase enzymes

Anticancer Antibiotics

These are cell cycle non-specific except for bleomycin. These agents intercalate with DNA disrupting its function and also generate free radicals, which exert other cytotoxic action.

- Dactinomycin—It is one among the most potent anti-tumour agent known. It intercalates between adjacent guanine–cytosine base pairs along minor groove and blocks transcription of DNA by RNA polymerase. It also makes single strand breaks by free radical intermediate or topoisomerase II function.
- Anthracyclines—Form complex with topoisomerase II and DNA, inhibiting re-ligation leading to apoptosis. They also form free radical intermediates that oxidise DNA bases leading to apoptosis. Mitoxantrone has structural similarity and less cardiotoxic than other anthracyclines.

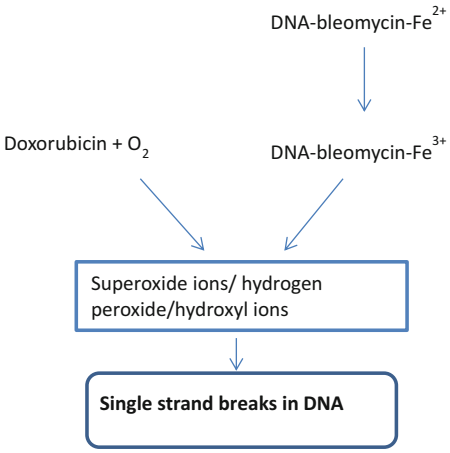

Fig. 63.6 Mechanism of antitumour antibiotics

- Bleomycin—It is a mixture of bleomycins A2 and B2. It generates free radicals which open deoxyribose at 3′ position producing single and double stranded breaks in DNA (Fig. 63.6).
- Mitomycin—It undergoes intracellular enzymatic or spontaneous chemical alteration to bifunctional or trifunctional alkylating agents. These form cross-links between adenine (N6) and guanine (O6 and N7) leading to inhibition of DNA synthesis.

Miscellaneous

- Mitotane—Chemically similar to dichlorodiphenyltrichloroethane (DDT). Its mechanism is not well known. It causes selective destruction of adrenocortical cells.
- Trabectedin—It acts as alkylating agent and forms DNA adducts. This is recognised by the NER complex and leads to double strand break in the attempt to repair it.
- L-Asparaginase—Leukemic lymphocytes lack enough asparaginase synthase for L asparagine. Hence, it obtains the amino acids from plasma. L-asparaginase catalyses the hydrolysis of amino acids in the plasma, thus leading to cell death.
- Hydroxyurea (HU)—It inhibits the enzyme ribonucleotide reductase (RNR) which catalyses the conversion of ribonucleotides to deoxyribonucleotides. The drug is specific for S phase of cell cycle.
- Tretinoin (ATRA) and arsenic trioxide (ATO)—Induce differentiation of cells. ATO is also cytotoxic by increasing the concentration of ROS in leukemic cells.

63.3 Indications and Pharmacokinetics

Table 63.1 summarises the important indications and pharmacokinetics of cytotoxic drugs used in cancer treatment.

Table 63.1 Indications and pharmacokinetics of cytotoxic drugs

Drug	Indications	Pharmacokinetics
Meclorethamine	Topically for cutaneous T cell lymphoma Lymphoid malignancies, e.g. non-Hodgkin's lymphoma, Burkitt lymphoma	• Oral—cyclophosphamide, melphalan, chlorambucil, busulfan, lomustine; rest are all intravenous • Carmustine—wafer implants available • Nitrosoureas are highly lipid soluble and readily cross the blood–brain barrier; therefore, they are useful in the treatment of brain tumours • Except cyclophosphamide and ifosfamide, alkylating drugs have short half-lives; for example, mechlorethamine has a half-life of 10 min • Cyclophosphamide and ifosfamide—generate their alkylating species through hydroxylation by cytochrome P450 (CYP450) • Temozolomide is related to dacarbazine, unlike dacarbazine, temozolomide does not require the CYP450 system for metabolic trans formation, as it undergoes chemical transformation • It also inhibits the repair enzyme • Temozolomide differs from dacarbazinein that it crosses the blood–brain barrier • Temozolomideis administered intravenously or orally • Excreted through urine
Cyclophosphamide	Breast, ovarian, and solid tumours in children Autoimmune conditions like rheumatoid arthritis	
Ifosfamide	Germ cell testicular cancer First line treatment of sarcoma	
Melphalan	Multiple myeloma	
Chlorambucil	CLL	
Bendamustine	CLL, NHL	
Altretamine	Palliative care in ovarian cancer	
Busulphan	CML	
Carmustine, temozolomide	Brain tumours (gliomas)	
Streptozocin	Pancreatic islet cell carcinoma and carcinoid tumours	
Dacarbazine	Hodgkin's disease	
Procarbazine	Hodgkin's disease (MOPP regimen), melanoma Gliomas (PCV regimen)	
Cisplatin, carboplatin	Ovarian, head and neck, bladder, oesophagus, lung, colon, cervix, endometrial cancer	• Renal elimination—dose adjustment required
Oxaliplatin	Colorectal and gastric cancer	

(continued)

Table 63.1 (continued)

Drug	Indications	Pharmacokinetics
Methotrexate	Childhood ALL, meningeal lymphoma/carcinomatosis, choriocarcinoma	• MTX has erratic absorption from GI at low doses. Does not penetrate BBB. Can be given intrathecally, intravenous, and intramuscularly. Excretion is primarily by urine. Its 7-OH metabolite is less water soluble so its urine must be alkaline and patient well hydrated to prevent renal toxicity • High-dose regimens of methotrexate may require rescue with folinic acid, also known as leucovorin • 5-FU is given IV or topically due to severe gastrointestinal toxicity • It is metabolised in liver • Capecitabine is a prodrug of 5-FU which can be given orally. Excreted via urine • Purine analogues undergo metabolism in the liver. 6-MP is metabolised by xanthine oxidase, so allopurinol can increase toxicity • Other drugs are excreted via urine and dose adjustment required in renal impairment
5-Fluorouracil	Colorectal cancer—FOLFOX/ FOLFIRINOX regimen	
Floxuridine	Metastatic carcinoma of colon	
Capecitabine	Metastatic breast and colorectal carcinoma	
Trifluridine	Metastatic colorectal carcinoma along with tipiracil	
Cytarabine	AML	
Azacitidine	MDS	
Gemcitabine	Metastatic pancreatic, NSCLC, ovarian, bladder cancer	
6-TG and 6-MP	ALL	
Fludarabine	CLL	
Cladribine	Hairy cell leukaemia, CLL, low-grade lymphomas	
Clofarabine	Paediatric ALL	
Nelarabine	Acute T cell leukaemia	
Pentostatin	Hairy cell leukaemia	
Vinblastine	Testicular cancer, HL–ABVD regimen Kaposi sarcoma, neuroblastoma, Langerhans cell histiocytosis, bladder cancer, carcinoma breast, choriocarcinoma, Leukaemias, Wilms tumour	• Risk of hyperuricemia due to rapid cytotoxic effect on IV administration. Excreted via hepatic pathway • Taxanes and vinca alkaloids require dose modification in hepatic impairment • Epothilones—administered IV and cleared by hepatic route • Topotecan given IV follows linear pharmacokinetics. Requires dose reduction in renal disease. Low PPB so better CNS penetration • Irinotecan is a prodrug converted by carboxylesterases in liver to SN-38, having AUC of 4%. More active form and half-life compared to topotecan. Also it has no CNS penetration and excreted via hepatic route
Vincristine	NHL–CHOP regimen	
Vinorelbine	NSLC, breast cancer	
Eribulin	Liposarcoma and drug resistant metastatic breast cancer	
Taxanes	Metastatic ovarian, breast, lung, gastrointestinal, genitourinary, head and neck	
Epothilones	Hormone refractory metastatic prostate cancer (cabazitaxel, estramustine)	
Camptothecins	Ovarian and SCLC (topotecan) Breast cancer Colorectal cancer, SCLC, metastatic pancreatic cancer, FOLFIRI/FOLFIRINOX regimens (irinotecan)	

(continued)

Table 63.1 (continued)

Drug	Indications	Pharmacokinetics
Dactinomycin	Children—rhabdomyosarcoma, Wilms tumour—curative Ewing, Kaposi, sarcoma Adults—curative in choriocarcinoma	• IV route, no CNS penetration • Doxorubicin is a prodrug, and idarubicin is the active metabolite • Eliminated through hepatic metabolism • Idarubicin is the only anthracycline that can be given orally
Doxorubicin, epirubicin	Solid tumours—ovarian, breast, sarcomas	
Daunorubicin, Idarubicin	AML	
Mitoxantrone	Prostate cancer, AML	
Valrubicin	Bladder cancer	
Bleomycin	HL, germ cell tumour of testis (curative) and ovary	• Bleomycin is a large cation and therefore has difficulty penetrating cell membranes. It enters cells through a special membrane binding protein • It is administered parenterally, either intravenously or by the intramuscular or subcutaneous route. Bleomycin can also be instilled directly into the bladder • Excreted via kidneys
Mitomycin	Anal cancer-curative, transitional cell cancer	• Instilled into bladder
L-asparaginase	ALL	• Given IM/IV. Pegylated form available with half-life of 6–7 days vs 1 day and has less immunogenicity • HU—oral comparable with IV, crosses blood–brain barrier, excreted via renal route • ATRA—orally given, excreted via hepatic route • ATO—given IV, eliminated via enzymatic methylation. No dose modification required in hepatic or renal disease
Hydroxyurea	CML, PCV, essential thrombocytosis, sickle cell disease	
Retinoids	APML	

Abbreviations: *CLL* chronic lymphocytic leukaemia, *HL* Hodgkin's lymphoma, *NHL* non-Hodgkin's lymphoma, *CML* chronic myeloid leukaemia, *ALL* acute lymphocytic leukaemia, *MDS* myelodysplastic syndrome, *IV* intravenous, *CNS* central nervous system, *AUC* area under curve, *PCV* polycythemia vera, *APML* acute pro-myelocytic leukaemia, *SCLC* small cell lung cancer, *NSCLC* non-small cell lung cancer, *5-FU* 5-fluorouracil, *HU* hydroxyurea, *ATRA* tretinoin, *ATO* arsenic trioxide, *MOPP* mechlorethamine, vincristine, procarbazine, and prednisone, *ABVD* doxorubicin, bleomycin, vinblastine, and dacarbazine, *FOLFIRINOX* FOL—folinic acid, F—5-fluorouracil, Irin—irinotecan, Ox—oxaliplatin, *FOLFIRI* folinic acid, 5-fluorouracil, irinotecan, *FOLFOX* folinic acid fluorouracil, oxaliplatin, *PCV* procarbazine, lomustine (CCNU), vincristine, *CHOP* cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine (Oncovin), prednisolone

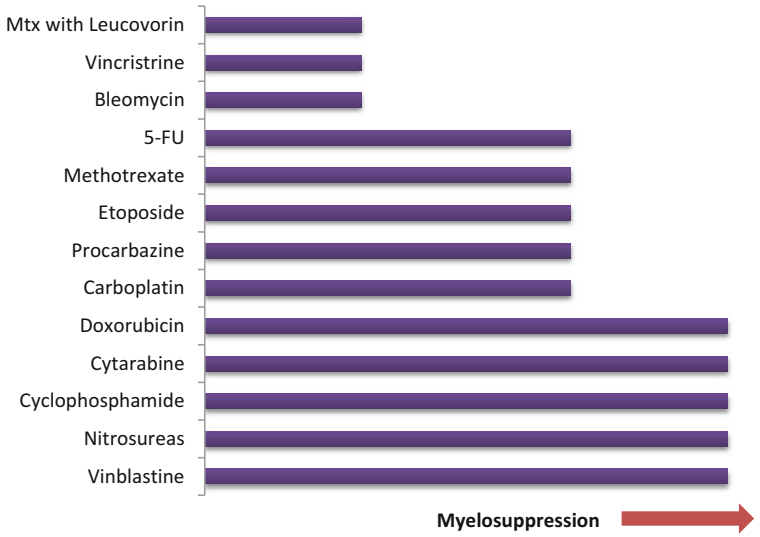

Fig. 63.7 Risk of myelosuppression associated with various drugs

63.4 Adverse Drug Reactions (ADRs)

Common ADRs to cytotoxic drugs—nausea, vomiting, alopecia, mucositis, stomatitis, and myelosuppression.

- Methotrexate (high dose or chronic therapy) given with folinic acid reduces risk of myelosuppression, mucositis, and alopecia.

Figure 63.7 gives the risk of myelosuppression associated with various drugs

A few examples of adverse reactions characteristic of each drug are given in Table 63.2.

Table 63.2 Characteristic toxicities observed with cytotoxic agents

Adverse drug reaction	Drug
Pulmonary toxicity	Nitrosoureas, busulfan, bleomycin
Nephrotoxicity	Cyclophosphamide, Ifosphamide Platinum compounds reduced by pre-treatment and amifostine
Haemorrhagic cystitis	Cyclophosphamide, Ifosphamide due to toxic metabolites like acrolein. Managed by mesna or N-acetyl cysteine
Neurotoxicity	Ifosphamide due to chloroacetaldehyde
Secondary leukaemia	Most of alkylating agents
Soft tissue necrosis (extravasation), cardiotoxicity (acute and chronic types)	Anthracyclines
Pneumonitis, nephrotoxicity, dermatitis, defective oogenesis/spermatogenesis, hepatic impairment	Folate antagonists
Red itchy rash	Pemetrexed
Cutaneous side effects—hyperpigmentation, hyperkeratosis, erythema, ulcer Interstitial pneumonitis and hypersensitivity reactions (serious ADR)	Bleomycin
Hand and foot syndrome	Capecitabine, 5-FU
Diarrhoea	Gemcitabine, irinotecan
Serious hypersensitivity reaction	Paclitaxel
Phlebitis/cellulitis Peripheral neuropathy, constipation Myelosuppression	Vinblastine/vincristine Vincristine Vinblastine
Vesicant property	Mechlorethamine
Ototoxicity Peripheral neuropathy	Platinum compounds (more with cisplatin) Dose limiting toxicity of oxaliplatin
Hyperglycaemia, clotting abnormalities	L-Asparaginase
Leukocyte maturation syndrome Hypercalcemia, renal failure QT prolongation	ATRA, ATO ATRA ATO

ATRA tretinoin, *ATO* arsenic trioxide

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