Cancer Chemotherapy

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- Cancer continues to be the second leading cause of mortality from disease in the USA, accounting for nearly 500,000 deaths in 2008.

- Cancer is a disease characterized by a loss in the normal control mechanisms that govern cell survival, proliferation, and differentiation.

CAUSES OF CANCER

The incidence is related to multiple factors:

- Gender,
- Age,
- Race,
- genetic predisposition,
- exposure to environmental carcinogens.
  - Ionizing radiation
  - Chemical carcinogens (azo dyes, aflatoxins, asbestos, benzene)

CAUSES OF CANCER

- Viruses
  - Hep B & hep C are associated with the development of hepatocellular cancer
  - HIV is associated with Hodgkin's & non-Hodgkin's lymphomas
  - Human papillomavirus is associated with cervical cancer
  - Ebstein-Barr virus is associated with nasopharyngeal cancer.

CAUSES OF CANCER

- Oncogenes code for specific growth factors
  - If amplified or mutated can lead to constitutive overexpression in malignant cells
  - The bcl -2 family of genes represents a series of pro-survival genes that promotes survival by directly inhibiting apoptosis.

- Tumor suppressor genes, may be deleted or mutated, & can give rise to the neoplastic phenotype
  - The p53 gene is a tumor suppressor gene, & play an important role in suppressing neoplastic transformation.
  - p53 is mutated in up to 50% of all human solid tumors, including liver, breast, colon, lung, cervix, bladder, prostate, and skin.

Chemotherapy is presently used in three main clinical settings:

- Primary induction treatment
  - Advanced disease
  - Cancers with other effective treatment approaches
- Neoadjuvant treatment
  - Patients who present with localized disease
  - Patients in whom surgery or radiation, are inadequate
- Adjuvant treatment
  - The goal of chemotherapy in it is to reduce the incidence of both local and systemic recurrence and to improve the overall survival of patients.

CELL CYCLE KINETICS & ANTICANCER EFFECT

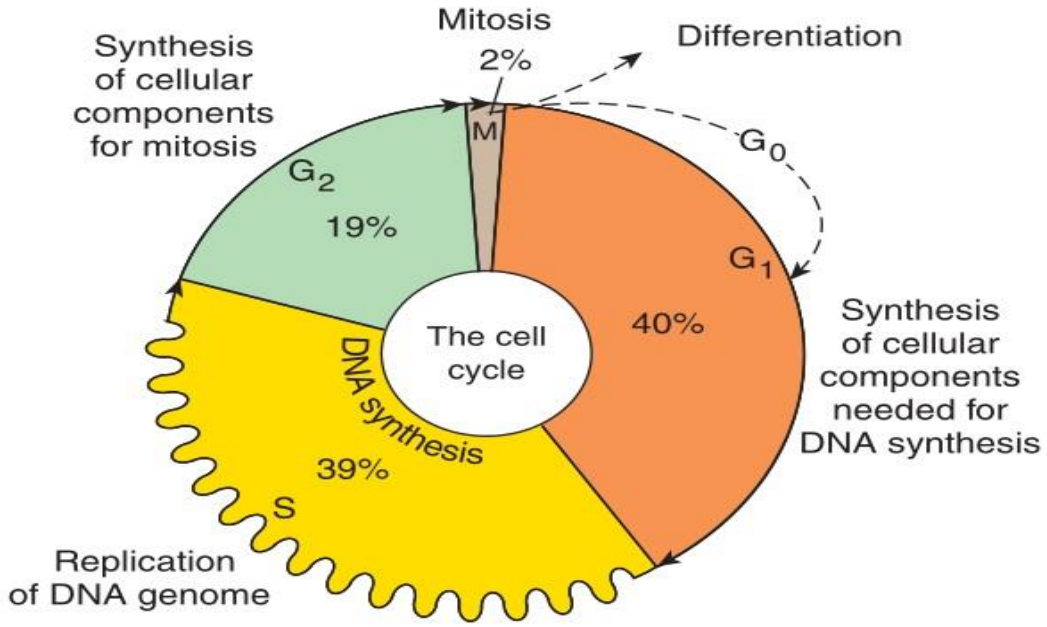

FIGURE 54–2 The cell cycle and cancer. A conceptual depiction of the cell cycle phases that all cells—normal and neoplastic—must traverse before and during cell division. The percentages given represent the approximate percentage of time spent in each phase by a typical malignant cell; the duration of G_1, however, can vary markedly. Many of the effective anticancer drugs exert their action on cells traversing the cell cycle and are called cell cycle-specific (CCS) drugs (see Table 54–1). A second group of agents called cell cycle-nonspecific (CCNS) drugs can sterilize tumor cells whether they are cycling or resting in the G_0 compartment. CCNS drugs can kill both G_0 and cycling cells (although cycling cells are more sensitive).

CELL CYCLE KINETICS & ANTICANCER EFFECT

TABLE 54–1 **Cell cycle effects of major classes of anticancer drugs.**

Cell Cycle-Specific (CCS) Agents	Cell Cycle-Nonspecific (CCNS) Agents
Antimetabolites (S phase)	**Alkylating agents**
Capecitabine	Altretamine
Cladribine	Bendamustine
Clofarabine	Busulfan
Cytarabine (ara-C)	Carmustine
Fludarabine	Chlorambucil
5-Fluorouracil (5-FU)	Cyclophosphamide
Gemcitabine	Dacarbazine
6-Mercaptopurine (6-MP)	Lomustine
Methotrexate (MTX)	Mechlorethamine
Nelarabine	Melphalan
Pralatrexate	Temozolomide
6-Thioguanine (6-TG)	Thiotepa
Epipodophyllotoxin (topoisomerase II inhibitor) (G_1–S phase)	**Antitumor antibiotics**
Etoposide	Dactinomycin
Taxanes (M phase)	Mitomycin
Albumin-bound paclitaxel	**Camptothecins (topoisomerase I inhibitors)**
Cabazitaxel	Irinotecan
Paclitaxel	Topotecan
Vinca alkaloids (M phase)	**Platinum analogs**
Vinblastine	Carboplatin
Vincristine	Cisplatin
Vinorelbine	Oxaliplatin
Antimicrotubule inhibitor (M phase)	**Anthracyclines**
Ixabepilone	Daunorubicin
Antitumor antibiotics (G_2–M phase)	Doxorubicin
Bleomycin	Epirubicin
	Idarubicin
	Mitoxantrone

CANCER CHEMOTHERAPEUTIC DRUGS

- ALKYLATING AGENTS
- ANTIMETABOLITES
- NATURAL PRODUCT CHEMOTHERAPY DRUGS
- ANTITUMOR ANTIBIOTICS
- MISCELLANEOUS
  - IMATINIB, DASATINIB, etc.

ALKYLATING AGENTS

- Heterogenous group of loosely related compounds:
  - Nitrogen mustards (Mechlorethamine, cyclophosphamide, ifosfamide)
  - Ethyleneimines (thiotepa, altretamine)
  - Alkyl sulfonates (Busulfan)
  - Nitrosureas (Carmustine)
  - Triazenes (Dacarbazine)
- MOA: Form highly reactive carbonium ion intermediates which covalently link to amines, oxygens, or phosphates of DNA
  - N7 of guanine is highly susceptible
  - Other targets include N1 and N3 of adenine, N3 of cytosine and O6 of guanine
- Cell will then either try to repair the DNA and undergo cell cycle arrest
  - In cases where this does not work it will then undergo apoptosis

MOA

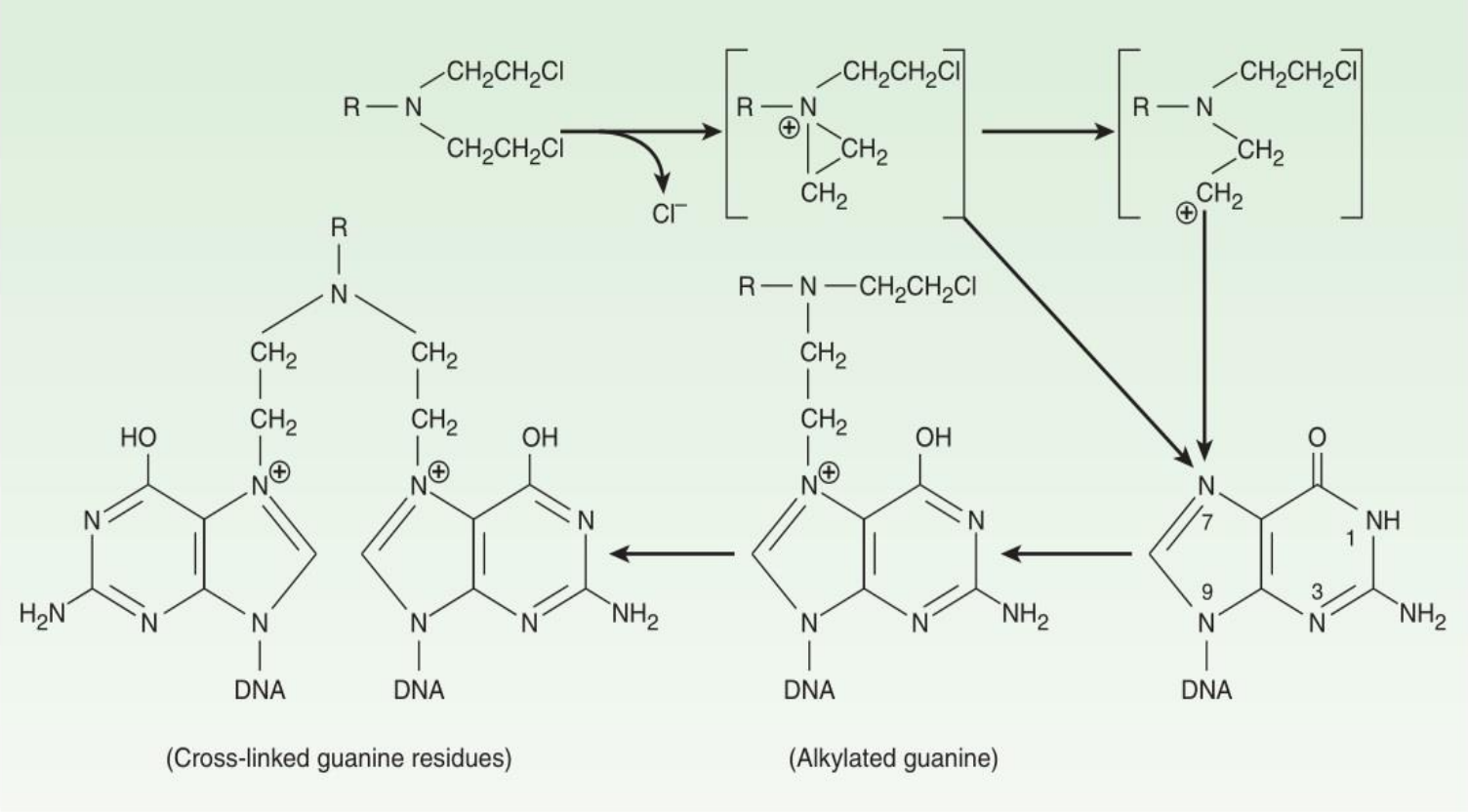

FIGURE 54–4 Mechanism of alkylation of DNA guanine. A bis(chloroethyl)amine forms an ethyleneimonium ion that reacts with a base such as N7 of guanine in DNA, producing an alkylated purine. Alkylation of a second guanine residue, through the illustrated mechanism, results in cross-linking of DNA strands.

ALKYLATING AGENTS

- Uses: extensive
  - Solid Tumors: Breast cancers, prostate cancers, sarcomas, etc
  - Heme malignancies: leukemias, lymphomas, myeloma
  - Non-malignant conditions: rheumatic diseases
- Commonly used with cell cycle dependent agents
- Resistance:
  - Decreased permeation of active transported drugs
  - Increased concentrations of nucleophillic substances that bind and inactivate agents
  - Increased MMR and repair mechanisms

Cyclophosphamide (Cytoxan)

- One of the most extensive agents used in therapy
  - Given IV and PO
- Prodrug: a drug that is converted in the body to an active metabolite
  - Phosphoramide mustard
- Acrolein is toxic and causes hemorrhagic cystitis
- Used over a variety of diseases including
  - Rheumatic disease
  - Solid tumors
  - Heme malignancies

Cyclophosphamide Metabolism

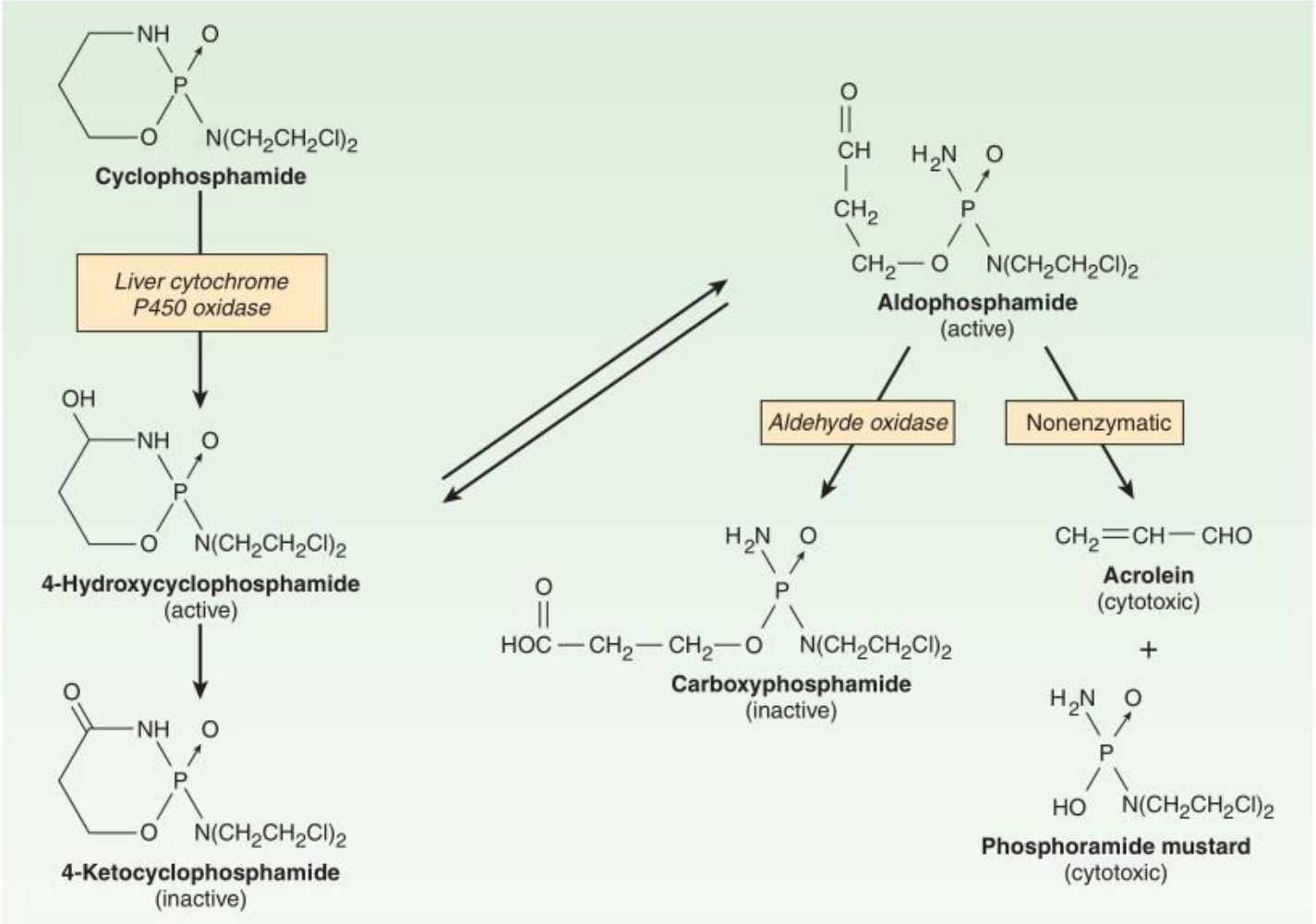

FIGURE 54–5 Cyclophosphamide metabolism.

Platinum Complexes

- Behave similar to alkylating agents without alkylation
- MOA: Covalently bind on nucleophillic sites of DNA
  - The chloride, cyclohexane and oxalate molecules are displaced by water leaving a highly positively charged molecule
- Cis/carboplatin share similar activity and are somewhat interchangeable
- Resistance:
  - Cis/carboplatin share cross-resistance, while oxaliplatin does not
  - Loss of function of MMR proteins which would induce protein
  - Up-regulation of DNA repair genes

Platinum Complexes

- Spectrum of activity:
  - Cis/carboplatin: Solid tumor primarily
  - SCLC, NSCLC, Head and Neck, Bladder, Testicular
- Oxaliplatin: GI tract cancers (Gastric, Pancreatic, CRC)
- Toxicities:
  - Cis/carboplatin:
  - Renal toxicity: Cisplatin more so
  - Myelosuppression: carboplatin more so (thrombocytopenia)
- Oxaliplatin:
  - Peripheral Neurotoxicity
  - Myelosuppression: thrombocytopenia

TABLE 54–2 Alkylating agents and platinum analogs: Clinical activity and toxicities.

Alkylating Agent	Mechanism of Action	Clinical Applications	Acute Toxicity	Delayed Toxicity
Mechlorethamine	Forms DNA cross-links, resulting in inhibition of DNA synthesis and function	Hodgkin's and non-Hodgkin's lymphoma	Nausea and vomiting	Moderate depression of peripheral blood count; excessive doses produce severe bone marrow depression with leukopenia, thrombocytopenia, and bleeding; alopecia and hemorrhagic cystitis occasionally occur with cyclophosphamide; cystitis can be prevented with adequate hydration; busulfan is associated with skin pigmentation, pulmonary fibrosis, and adrenal insufficiency
Chlorambucil	Same as above	CLL and non-Hodgkin's lymphoma	Nausea and vomiting	
Cyclophosphamide	Same as above	Breast cancer, ovarian cancer, non-Hodgkin's lymphoma, CLL, soft tissue sarcoma, neuroblastoma, Wilms' tumor, rhabdomyosarcoma	Nausea and vomiting	
Bendamustine	Same as above	CLL, non-Hodgkin's lymphoma	Nausea and vomiting	
Melphalan	Same as above	Multiple myeloma, breast cancer, ovarian cancer	Nausea and vomiting	
Thiotepa	Same as above	Breast cancer, ovarian cancer, superficial bladder cancer	Nausea and vomiting	
Busulfan	Same as above	CML	Nausea and vomiting	
Carmustine	Same as above	Brain cancer, Hodgkin's and non-Hodgkin's lymphoma	Nausea and vomiting	Myelosuppression; rarely interstitial lung disease and interstitial nephritis
Lomustine	Same as above	Brain cancer	Nausea and vomiting	
Altretamine	Same as above	Ovarian cancer	Nausea and vomiting	Myelosuppression, peripheral neuropathy, flu-like syndrome
Temozolomide	Methylates DNA and inhibits DNA synthesis and function	Brain cancer, melanoma	Nausea and vomiting, headache and fatigue	Myelosuppression, mild elevation in liver function tests, photosensitivity
Procarbazine	Methylates DNA and inhibits DNA synthesis and function	Hodgkin's and non-Hodgkin's lymphoma, brain tumors	Central nervous system depression	Myelosuppression, hypersensitivity reactions
Dacarbazine	Methylates DNA and inhibits DNA synthesis and function	Hodgkin's lymphoma, melanoma, soft tissue sarcoma	Nausea and vomiting	Myelosuppression, central nervous system toxicity with neuropathy, ataxia, lethargy, and confusion
Cisplatin	Forms intrastrand and interstrand DNA cross-links; binding to nuclear and cytoplasmic proteins	Non-small cell and small cell lung cancer, breast cancer, bladder cancer, cholangiocarcinoma, gastroesophageal cancer, head and neck cancer, ovarian cancer, germ cell cancer	Nausea and vomiting	Nephrotoxicity, peripheral sensory neuropathy, ototoxicity, nerve dysfunction
Carboplatin	Same as cisplatin	Non-small cell and small cell lung cancer, breast cancer, bladder cancer, head and neck cancer, ovarian cancer	Nausea and vomiting	Myelosuppression; rarely peripheral neuropathy, renal toxicity, hepatic dysfunction
Oxaliplatin	Same as cisplatin	Colorectal cancer, gastroesophageal cancer, pancreatic cancer	Nausea and vomiting, laryngopharyngeal dysesthesias	Myelosuppression, peripheral sensory neuropathy, diarrhea

CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia.

ANTIMETABOLITES

TABLE 54–3 Antimetabolites: Clinical activity and toxicities.

Drug	Mechanism of Action	Clinical Applications	Toxicity
Capecitabine	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Breast cancer, colorectal cancer, gastroesophageal cancer, hepatocellular cancer, pancreatic cancer	Diarrhea, hand-foot syndrome, myelosuppression, nausea and vomiting
5-Fluorouracil	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Colorectal cancer, anal cancer, breast cancer, gastroesophageal cancer, head and neck cancer, hepatocellular cancer	Nausea, mucositis, diarrhea, bone marrow depression, neurotoxicity
Methotrexate	Inhibits DHFR; inhibits TS; inhibits de novo purine nucleotide synthesis	Breast cancer, head and neck cancer, osteogenic sarcoma, primary central nervous system lymphoma, non-Hodgkin's lymphoma, bladder cancer, choriocarcinoma	Mucositis, diarrhea, myelosuppression with neutropenia and thrombocytopenia
Pemetrexed	Inhibits TS, DHFR, and purine nucleotide synthesis	Mesothelioma, non-small cell lung cancer	Myelosuppression, skin rash, mucositis, diarrhea, fatigue, hand-foot syndrome
Cytarabine	Inhibits DNA chain elongation, DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of cytarabine triphosphate into DNA	AML, ALL, CML in blast crisis	Nausea and vomiting, myelosuppression with neutropenia and thrombocytopenia, cerebellar ataxia
Gemcitabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of gemcitabine triphosphate into DNA resulting in inhibition of DNA synthesis and function	Pancreatic cancer, bladder cancer, breast cancer, non-small cell lung cancer, ovarian cancer, non-Hodgkin's lymphoma, soft tissue sarcoma	Nausea, vomiting, diarrhea, myelosuppression
Fludarabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of fludarabine triphosphate into DNA; induction of apoptosis	Non-Hodgkin's lymphoma, CLL	Myelosuppression, immunosuppression, fever, myalgias, arthralgias
Cladribine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of cladribine triphosphate into DNA; induction of apoptosis	Hairy cell leukemia, CLL, non-Hodgkin's lymphoma	Myelosuppression, nausea and vomiting, and immunosuppression
6-Mercaptopurine (6-MP)	Inhibits de novo purine nucleotide synthesis; incorporation of triphosphate into RNA; incorporation of triphosphate into DNA	AML	Myelosuppression, immunosuppression, and hepatotoxicity
6-Thioguanine	Same as 6-MP	ALL, AML	Same as above

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; DHFR, dihydrofolate reductase; dNTP, deoxyribonucleotide triphosphate; FdUTP, 5-fluorodeoxyuridine-5′-triphosphate; FUTP, 5-fluorouridine-5′-triphosphate; TS, thymidine synthase.

ANTIMETABOLITES

ANTIFOLATES Methotrexate

- MOA: Dihydrofolate reductase (DHFR) inhibitor
  - Depletion of tetrahydrofolate, necessary for purine and thymidylate synthesis
- Resistance:
  - Decreased active transport into cell
  - Altered DHFR that impairs MTX binding or increased expression of DHFR
  - Increased efflux and active transport out of cells
- Side Effects:
  - Myelosuppression
  - Mucositis and intestinal inflammation
  - Nephrotoxicity
  - Neurotoxicity

Methotrexate Uses

- Used in all types of cancers and include autoimmune conditions as well
  - Control graft-versus-host disease
- Doses can be given orally, intravenously or intrathecally
- High-Dose Methotrexate (> 1 g/m 2 /dose)
  - Requires therapeutic blood monitoring
  - Use of leucovorin “rescue”
  - Requires urine alkylinization
  - Penetrates CNS

Pyrimidine & Purine Analogs

- 5-Fluorouracil: Pyrimidine Analog
- MOA: Prodrug, is somewhat rate dependent (depends how it is administered)
  - Continuous infusion: inhibition of thymidylate synthase leading to thymidine deficiency
  - Leucovorin is administered prior to starting to stabilize 5FU-TS complex
  - Bolus: False base integration into RNA and DNA
- Resistance:
  - Reduced conversion to active metabolite
  - Amplification of TS or alteration of TS binding site
  - Amplificiation of degrative enzymes

5-Fluorouracil

- Colon cancer: FOLFOX regimen
  - Oxaliplatin 85 mg/m 2 IV on day 1
  - Leucovorin 400 mg/m 2 IV given with oxaliplatin on day 1, followed by
  - 5-FU 400 mg/m 2 IV Bolus, then
  - 5-FU 2.4 g/m 2 IV given continuously over 46 hours

- Side effects:
  - Bolus: myelosuppression, angina
  - Continous: N/V, diarrhea, mucositis, hand-foot syndrome

- Antidote: uridine triacetate

Natural Products

EPIPODOPHYLLOTOXINS, TAXANES, VINCA ALKALOIDS,CAMPTOTHECANS

Vinca Alkaloids: Depolymerization

- Isolates from Catharanthus roseus (Madagascar periwinkle)
- MOA: Inhibition of polymerization by binding to β – tubulin and stabilizing it
  - Vincristine, vinblastine, vinorelbine
- Fatal if given intrathecally (No vines in the spine!)
- Side Effects:
  - Vesicant
  - Neurotoxicity: Vincristine
  - Peripheral neuropathy
  - GI: constipation
  - Myelosuppression
- Resistance:
  - P-gp upregulation

Anthracycline: Doxorubicin

- Antracyclines: anti-tumor antibiotics, isolated from S. peucetius
  - Class includes: daunorubicin, epirubicin, idarubicin
- MOA: Multiple. Prodrug (doxorubicinol)
  - Major: Topoisomerase II inhibition- prevents re-ligation of DNA
  - Minor: DNA intercalation, and prevention of free radical formation
- Resistance: Upregulation of P-gp (MDR1) that efluxes doxorubicin out

- Side Effects:
  - Cardiotoxicity (additive effects with concurrent cyclophosphamide)
  - Lifetime dosing limits
  - Myelosuppression
  - Alopecia
  - Mucositis/ N/V
  - Vesicant
- Red discoloration of: urine, tears, CNS fluid

Etoposide

- Extract from roots of Podophyllum peltatum (mandrake plant)
- MOA: Topoisomerase II inhibitor via stabilization of TOP2 complex
  - Accumulation of cells in S phase (G 2 Phase as well)
  - Leads to apoptosis
- Side Effects:
  - Myelosuppression
  - Alopecia
- Resistance:
  - P-gp up-regulation
  - Repair of DNA breaks
  - Alterations to Topoisomerase II

Taxanes: Polymerizing agents

- Discovered from Taxus brevifolia (Pacific Yew Tree)
- MOA: Inhibit depolarization by binding to β-tubulin, causing mitotic arrest
  - Paclitaxel, docetaxel, cabazitaxel, ixabepilone, nab-paclitaxel
- Drugs are extremely hydrophobic, use castor oil for dissolution
  - Caster Oil causes anaphylactic reactions

- Side Effects:
  - Myelosuppression
  - Alopecia: full body
  - Neuropathy
  - Myalgias
  - Edema
- Resistance:
  - P-gp up-regulation (substrate)
  - Alteration of tubulin structure

CAMPTOTHECINS Irinotecan

- Isolated from a Chinese tree Camptotheca acuminata
- MOA: Prodrug, Topoisomerase I inhibition
  - Active metabolite is SN-38
  - SN-38 is inactivated via UGT1A1
- Side effects:
  - DIARRHEA
  - Alopecia
  - Myelosuppression
- Resistance:
  - P-gp upregulation

TABLE 54–4 Natural product cancer chemotherapy drugs: Clinical activity and toxicities.

Drug	Mechanism of Action	Clinical Applications[1]	Acute Toxicity	Delayed Toxicity
Bleomycin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks	Hodgkin's and non-Hodgkin's lymphoma, germ cell cancer, head and neck cancer	Allergic reactions, fever, hypotension	Skin toxicity, pulmonary fibrosis, mucositis, alopecia
Daunorubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	AML, ALL	Nausea, fever, red urine (not hematuria)	Cardiotoxicity (see text), alopecia, myelosuppression
Docetaxel	Inhibits mitosis	Breast cancer, non-small cell lung cancer, prostate cancer, gastric cancer, head and neck cancer, ovarian cancer, bladder cancer	Hypersensitivity	Neurotoxicity, fluid retention, myelosuppression with neutropenia
Doxorubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	Breast cancer, Hodgkin's and non-Hodgkin's lymphoma, soft tissue sarcoma, ovarian cancer, non-small cell and small cell lung cancer, thyroid cancer, Wilms' tumor, neuroblastoma	Nausea, red urine (not hematuria)	Cardiotoxicity (see text), alopecia, myelosuppression, stomatitis
Etoposide	Inhibits topoisomerase II	Non-small cell and small cell lung cancer; non-Hodgkin's lymphoma, gastric cancer	Nausea, vomiting, hypotension	Alopecia, myelosuppression
Idarubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	AML, ALL, CML in blast crisis	Nausea and vomiting	Myelosuppression, mucositis, cardiotoxicity
Irinotecan	Inhibits topoisomerase I	Colorectal cancer, gastroesophageal cancer, non-small cell and small cell lung cancer	Diarrhea, nausea, vomiting	Diarrhea, myelosuppression, nausea and vomiting
Mitomycin	Acts as an alkylating agent and forms cross-links with DNA; formation of oxygen free radicals, which target DNA	Superficial bladder cancer, gastric cancer, breast cancer, non-small cell lung cancer, head and neck cancer (in combination with radiotherapy)	Nausea and vomiting	Myelosuppression, mucositis, anorexia and fatigue, hemolytic-uremic syndrome
Paclitaxel	Inhibits mitosis	Breast cancer, non-small cell and small cell lung cancer, ovarian cancer, gastroesophageal cancer, prostate cancer, bladder cancer, head and neck cancer	Nausea, vomiting, hypotension, arrhythmias, hypersensitivity	Myelosuppression, peripheral sensory neuropathy
Topotecan	Inhibits topoisomerase I	Small cell lung cancer, ovarian cancer	Nausea and vomiting	Myelosuppression
Vinblastine	Inhibits mitosis	Hodgkin's and non-Hodgkin's lymphoma, germ cell cancer, breast cancer, Kaposi's sarcoma	Nausea and vomiting	Myelosuppression, mucositis, alopecia, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), vascular events
Vincristine	Inhibits mitosis	ALL, Hodgkin's and non-Hodgkin's lymphoma, rhabdomyosarcoma, neuroblastoma, Wilms' tumor	None	Neurotoxicity with peripheral neuropathy, paralytic ileus, myelosuppression, alopecia, SIADH
Vinorelbine	Inhibits mitosis	Non-small cell lung cancer, breast cancer, ovarian cancer	Nausea and vomiting	Myelosuppression, constipation, SIADH

Anticancer antibiotics

- Dactinomycin, Doxorubicin & Daunorubucin
- Cell cycle non specific drugs
- Derived from streptomyces species
- MOA: Intercalation in the DNA between adjoining nucleotide pairs, blocks DNA & RNA synthesis, Generation of oxygen radicals which mediate single strand scission of DNA, Action on Topoisomerase II

Dactinomycin

- Uses: Wilms tumor, gestational choriocarcinoma

- Adverse effects:
  - bone marrow suppression
  - Irritant like meclorethamine
  - sensitizes to radiation, and inflammation at sites of prior radiation therapy may occur
  - Gastrointestinal adverse effects

- Doxorubicin:
  - Used in acute leukemias, malignant lymphoma and many solid tumors, direct instillation in bladder cancer
- Daunorubicin:
  - Use limited to ALL and granulocytic leukemias
- Toxicity:
  - Both cause cardiotoxicity (cardiomyopathy)
  - Marrow Depression, Alopecia

Bleomycin

- Uses :
  - Epidermoid cancers of skin, oral cavity, genitourinary tract, esophagus
  - Testicular tumors, Hodgkins lymphoma

- Adverse effects:
  - Pneumonitis
  - Fatal pulmonary fibrosis
  - Hyper pigmentation

Hormones & antagonists

- Corticosteroids
- Progestins
- Prednisolone
- Hydroxyprogesterone
- Estrogens
- Anti-androgens, Ethinyl Estradiol, Flutamide
- Tamoxifene, Toremifene
- Finasteride, Fulvestrant dutasteride

Glucocorticoids

- Marked lympholytic effect so used in acute leukaemias & lymphomas
- They also, Have Anti-inflammatory effect, Increase appetite, prevent anemia
- Produce sense of well being, Increase body weight, Supress hypersensitivity reaction
- Control hypercalcemia & bleeding, Non specific antipyretic effect
- Increase antiemetic effect of ondansetron

Tamoxifen

- DOSE:10-20mg bd
- Standard hormonal treatment in breast cancer
- Adverse effects:
  - Hot flushes , vomiting, vaginal bleeding, menstrual irregularities
  - venous thromboembolism, dermatitis, rarely endometrial cancer

Newer anticancer drugs

- Inhibitors of growth factors receptors
  - Imatinib: CML (BCR-ABL gene)
  - Gefitinib: Non small cell cancer of lungs (EGFR)
  - Nilotinib: CML (Tyrosine kinase inhibitor)
  - Dasatinib: CML (Tyrosine kinase inhibitor)
  - Lapatinib: metastatic breast cancer (HER2/neu)
  - Sunitinib: renal cell carcinoma (VEGF)
  - Sorafinib: renal cell carcinoma (VEGF)

Newer anticancer drugs

- Monoclonal antibodies

- Trastuzumab: breast cancer (HER2/neu)
- Bevacizumab: metastatic colon cancer (VEGF)
- Rituximab: non hodgkins lymphoma (CD-20)
- Panitumumab: metastatic colon cancer (EGFR)
- Alemtuzumab: CLL (CD 52 antigen)
- Iodine tositumonab: Non hodgkins (CD-20)

Chemotherapy Regimens

- Agents *obviously* need to be active against a given tumor
- Select agents with different:
  - MOA
  - Resistance
  - Dose-limiting toxicity
- Combinations needed to maximize kill and limit resistance
- Example:
  - CHOP Regimen

Chemotherapy Regimens

- Regimen known as CHOP is a cure for lymphomas even in stage IV

- C: Cyclophosphamide: alkylation of DNA (non-specific)
  - Myelosuppression, NV, Renal dysfunction, alopecia
- H: Doxorubicin: Topoisomerase II inhibitor (S-phase)
  - Cardiotoxicity, NV, myelosuppression, mucositis
- O: Vincristine: Antimitotic agent (M-Phase)
  - Neuropathy
- P: Prednisone: Not covered but immunosuppression
  - Increased appetite, hyperglycemia, hypertension

Cure or Increased Survival

Type of Cancer	*Chemotherapy*	*Results*
Gestational trophoblastic tumors	Methotrexate, dactinomycin, vinblastine	70% cured
Burkitt's tumor	Cyclophosphamide (many others)	50% cured
Testicular tumors (nonseminoma)	Dactinomycin, Methotrexate chlorambucil, Bleomycin, Cis-platinum diamine dichloride	70–80% respond; 2–3% cured
Wilms' tumor	Dactinomycin plus vincristine with surgery and radiotherapy	30–40% cured
Neuroblastoma	Cyclophosphamide with surgery and/or radiotherapy	5% cured
Acute lymphoblastic leukemia	Daunorubicin, prednisone, vincristine, 6-mercaptopurine, Methotrexate, BCNU	90% remission; 70% survive beyond 5 years
Hodgkin's disease, stage IIIB and IV	MOPP, ABVD	70% respond; 40% survive beyond 5 years

(*Note*: Adapted from I H Krakoff, Cancer Chemotherapeutic Agents, *Ca-A Cancer Journal of Clinicians*, 27, 1977, 132.)
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Palliation and Prolongation of Life

Type of Cancer	*Chemotherapy*	*Results*
Prostate carcinoma	Estrogens, castration, cyclophosphamide	70% respond with some prolongation of life
Breast carcinoma	Androgens, estrogens, alkylating agents, 5-fluorouracil, vincristine, prednisone, Methotrexate, Adriamycin	60–80% respond with probable prolongation of life
Chronic lymphocytic leukemia	Prednisone, alkylating agents	50% respond with probable prolongation of life
Lymphosarcoma	Prednisone, alkylating agents	50% respond with probable prolongation of life
Acute myeloblastic leukemia	Cytosine arabinoside and thioguanine	65% remission with prolongation of life

(Note: Adapted from IH Krakoff, Cancer Chemotherapeutic Agents, *Ca-A Cancer Journal of Clinicians*, 27, 1977, 132.)
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- Thank you