ANTICANCER DRUGS

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ANTICANCER DRUGS
The cancer cells once formed the cancer killing Natural Killer Cells (NK-Cells) and Anti-Cancer Lymphocytes immediately multiply and kill the cancer cells.
GENERAL PRINCIPLES IN CHEMOTHERAPY OF CANCER

- Bacterial metabolism differs markedly from that of host. While in malignant cells in fact host cell with minor differences therefore selectively is limited.

- Infecting microorganisms are amenable to immunological and other host defence mechanisms. This is absent or minimal with malignant cells.
A single colonogenic malignant cell is capable of producing progeny that can kill the host therefore ALL MALIGNANT CELLS MUST BE KILLED OR REMOVED

Drugs kill cancer cells by first order kinetics
When Immunotherapy is combined with conventional treatments, the immune system becomes multifold stronger to fight the cancer cells.

NK Cell

Lymphocyte

AIET
PBMCs (Peripheral Blood Mononuclear Cells)

NK Cell Multiplication

Re-infusion

Lymphocyte Multiplication & Activation

As the patients own immune cells are transfused back, this does not cause any allergy; therefore very safe.
Drug regimens which can effectively palliative large tumor burdens may be curative when applied to minute residual tumor cell population after surgery/irradiation. This is the basis of the combined modality approach.
Complete remission should be the goal of cancer chemotherapy:

- Drug are used in maximum tolerated doses. Combination of 2-6 drugs are given in intermittent pulses to achieve total cell kill – giving time in between for normal cells to recover.
Figure 51–1. Summary of the mechanisms and sites of action of some chemotherapeutic agents useful in neoplastic disease. PALA = N-phosphonoacetyl-L-aspartate; TMP = thymidine monophosphate.
Figure 51-2. The cell cycle and the relationship of antitumor drug action to the cycle. G₁ is the gap period between mitosis and the beginning of DNA synthesis. Resting cells (cells that are not preparing for cell division) are said to be in a subphase of G₁, G₀. S is the period of DNA synthesis, G₂ the premitotic interval, and M the period of mitosis. Examples of cell cycle-dependent anticancer drugs are listed in blue below the phase in which they act. Drugs that are cytotoxic for cells at any point in the cycle are called cycle-phase-nonspecific drugs. (Modified from Pratt et al., 1994 with permission.)
GENERAL TOXICITY OF CYTOTOXIC DRUGS

- Nausea and vomiting
- Alopecia
- oligozoospermia
- Impotence
- Amenorrhoea
- Abortion
- Carcinogenicity
- Hyperuricemia
- Opportunistic infections.
- Cystitis, alopecia – cyclophosphamide
- Neuropathy - vincristine
- Cardiac toxicity – doxorubicin
- Pulmonary fibrosis – bleomycin and busulfan
- Cisplatin – Nephrotoxicity
- Methotrexate – Megaloblastic anemia & pancytopenia
# Chemotherapeutic Agents Useful in Neoplastic Disease

<table>
<thead>
<tr>
<th>CLASS</th>
<th>TYPE OF AGENT</th>
<th>NONPROPRIETARY NAMES (OTHER NAMES)</th>
<th>DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>Nitrogen mustards</td>
<td>Mechloretamine</td>
<td>Hodgkin’s disease; non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclophosphamide</td>
<td>Acute and chronic lymphocytic leukemia; Hodgkin’s disease; non-Hodgkin’s lymphoma; multiple myeloma; neuroblastoma; breast, ovary, lung cancer; Wilms’ tumor; cervix, testis cancer; soft-tissue sarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ifosfamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Melphalan (L-sarcolysin)</td>
<td>Multiple myeloma; breast, ovarian cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chlorambucil</td>
<td>Chronic lymphocytic leukemia; primary macroglobulinemia; Hodgkin’s disease; non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td></td>
<td>Ethyleneimines and methylmelamines</td>
<td>Altretamine</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiotepa</td>
<td>Bladder, breast, ovarian cancer</td>
</tr>
<tr>
<td>Chemical Group</td>
<td>Drugs</td>
<td>Indicated Diseases</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
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<td>------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Methylhydrazine derivative</td>
<td>Procarbazine (N-methylhydrazine, MIH)</td>
<td>Hodgkin’s disease</td>
<td></td>
</tr>
<tr>
<td>Alkyl sulfonate</td>
<td>Busulfan</td>
<td>Chronic myelogenous leukemia</td>
<td></td>
</tr>
<tr>
<td>Nitrosoureas</td>
<td>Carmustine (BCNU)</td>
<td>Hodgkin’s disease; non-Hodgkin’s lymphoma; primary brain tumor; melanoma</td>
<td></td>
</tr>
<tr>
<td>Triazenes</td>
<td>Streptozocin (streptozotocin)</td>
<td>Malignant pancreatic insulinoma; malignant carcinoid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dacarbazine (DTIC; dimethyltriazenoimidazole carboxamide), temozolomide</td>
<td>Malignant melanoma; Hodgkin’s disease; soft-tissue sarcomas; glioma; melanoma</td>
<td></td>
</tr>
<tr>
<td>Platinum coordination complexes</td>
<td>Cisplatin, carboplatin, oxaliplatin</td>
<td>Testicular, ovarian, bladder, esophageal, lung, colon cancer</td>
<td></td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Folic acid analogs</td>
<td>Methotrexate (amethopterin)</td>
<td>Acute lymphocytic leukemia; choriocarcinoma; breast, head, neck, and lung cancer; osteogenic sarcoma; bladder cancer</td>
</tr>
<tr>
<td>----------------</td>
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<td>-----------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pyrimidine analogs</td>
<td>Pemetrexed</td>
<td></td>
<td>Mesothelioma, lung cancer</td>
</tr>
<tr>
<td></td>
<td>Fluorouracil (5-fluorouracil; 5-FU), capecitabine</td>
<td></td>
<td>Breast, colon, esophageal, stomach, pancreas, head and neck; premalignant skin lesion (topical)</td>
</tr>
<tr>
<td></td>
<td>Cytarabine (cytosine arabinoside)</td>
<td></td>
<td>Acute myelogenous and acute lymphocytic leukemia; non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Purine analogs and related inhibitors</td>
<td>Gemcitabine</td>
<td></td>
<td>Pancreatic, ovarian, lung cancer</td>
</tr>
<tr>
<td></td>
<td>Mercaptopurine (6-mercaptopurine; 6-MP)</td>
<td></td>
<td>Acute lymphocytic and myelogenous leukemia</td>
</tr>
<tr>
<td></td>
<td>Pentostatin (2′-deoxycoformycin), cladribine, fludarabine</td>
<td></td>
<td>Hairy cell leukemia; chronic lymphocytic leukemia; small cell non-Hodgkin’s lymphoma</td>
</tr>
</tbody>
</table>
### Table 51-1
Chemotherapeutic Agents Useful in Neoplastic Disease (Continued)

<table>
<thead>
<tr>
<th>CLASS</th>
<th>TYPE OF AGENT</th>
<th>NONPROPRIETARY NAMES (OTHER NAMES)</th>
<th>DISEASE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural</td>
<td>Vinca alkaloids</td>
<td>Vinblastine, vinorelbine</td>
<td>Hodgkin’s disease; non-Hodgkin’s lymphoma: breast, lung, and testis cancer</td>
</tr>
<tr>
<td>products</td>
<td></td>
<td>Vincristine</td>
<td>Acute lymphocytic leukemia; neuroblastoma; Wilms’ tumor; rhabdomyosarcoma; Hodgkin’s disease; non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Paclitaxel, docetaxel</td>
<td></td>
<td>Ovarian, breast, lung, bladder, head and neck cancer</td>
</tr>
<tr>
<td>Epipodophyllotoxins</td>
<td>Etoposide</td>
<td></td>
<td>Testis, small-cell lung, and other lung cancer; breast cancer; Hodgkin’s disease; non-Hodgkin’s lymphomas; acute myelogenous leukemia; Kaposi’s sarcoma</td>
</tr>
<tr>
<td></td>
<td>Teniposide</td>
<td></td>
<td>Same as etoposide; also acute lymphoblastic leukemia in children</td>
</tr>
<tr>
<td>Camptothecins</td>
<td>Topotecan, irinotecan</td>
<td></td>
<td>Ovarian cancer; small-cell lung cancer; colon and lung cancer</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Dactinomycin (actinomycin D)</td>
<td>Choriocarcinoma; Wilms’ tumor; rhabdomyosarcoma; testis; Kaposi’s sarcoma</td>
<td></td>
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<tr>
<td>-----------------------------</td>
<td>------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Daunorubicin (daunomycin, rubidomycin)</td>
<td>Acute myelogenous and acute lymphocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>Anthracenedione</td>
<td>Mitoxantrone</td>
<td>Soft-tissue, osteogenic, and other sarcoma; Hodgkin’s disease; non-Hodgkin’s lymphoma; acute leukemia; breast, genitourinary, thyroid, lung, stomach cancer; neuroblastoma and other childhood sarcoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bleomycin</td>
<td>Testis, and cervical cancer; Hodgkin’s disease; non-Hodgkin’s lymphoma</td>
<td></td>
</tr>
<tr>
<td>Enzymes</td>
<td>Mitomycin (mitomycin C)</td>
<td>Stomach, anal, and lung cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L-Asparaginase</td>
<td>Acute lymphocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous agents</td>
<td>Substituted urea</td>
<td>Hydroxyurea</td>
<td>Chronic myelogenous leukemia; polycythemia vera; essential thrombocytosis</td>
</tr>
<tr>
<td>-----------------------------------</td>
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<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Differentiating agents</td>
<td>Tretinoin, arsenic trioxide</td>
<td></td>
<td>Acute promyelocytic leukemia</td>
</tr>
<tr>
<td>Protein tyrosine kinase inhibitor</td>
<td>Imatinib</td>
<td></td>
<td>Chronic myelocytic leukemia; gastrointestinal stromal tumors; hypereosinophilia syndrome</td>
</tr>
<tr>
<td>Proteasome inhibitor</td>
<td>Gefitinib</td>
<td></td>
<td>Non-small-cell lung cancer</td>
</tr>
<tr>
<td></td>
<td>Bortezomib</td>
<td></td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>CLASS</td>
<td>TYPE OF AGENT</td>
<td>NONPROPRIETARY NAMES (OTHER NAMES)</td>
<td>DISEASE*</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------</td>
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<tr>
<td></td>
<td>Biological response</td>
<td>Interferon-alfa, interleukin 2</td>
<td>Hairy cell leukemia; Kaposi’s sarcoma; melanoma; carcinoid; renal cell; ovary; bladder; non-Hodgkin’s lymphoma; mycosis fungoides; multiple myeloma; chronic myelogenous leukemia; malignant melanoma</td>
</tr>
<tr>
<td></td>
<td>modifiers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibodies (see Tables 51-3 and 51-4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormones and antagonists</td>
<td>Adrenocortical suppressants</td>
<td>Adrenocorticosteroids</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------------------</td>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adrenocortical suppressants</td>
<td>Mitotane (o,p’-DDD)</td>
<td></td>
</tr>
<tr>
<td>Progestins</td>
<td>Aminogluthimide</td>
<td>Prednisone (several other equivalent preparations available; see Chapter 59)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydroxyprogesterone caproate, medroxyprogesterone acetate, megestrol acetate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogens</td>
<td>Diethylstilbestrol, ethinyl estradiol (other preparations available; see Chapter 57)</td>
<td>Adrenal cortex cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute and chronic lymphocytic leukemia; non-Hodgkin’s lymphoma; Hodgkin’s disease; breast cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrial, breast cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast, prostate cancer</td>
<td></td>
</tr>
<tr>
<td>Class</td>
<td>Examples</td>
<td>Disease</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>Anti-estrogens</td>
<td>Tamoxifen, toremifene</td>
<td>Breast cancer</td>
<td></td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>Anastrozole, letrozole, exemestane</td>
<td>Breast cancer</td>
<td></td>
</tr>
<tr>
<td>Androgens</td>
<td>Testosterone propionate, fluoxymesterone (other preparations available; see Chapter 58)</td>
<td>Breast cancer</td>
<td></td>
</tr>
<tr>
<td>Anti-androgen</td>
<td>Flutamide</td>
<td>Prostate cancer</td>
<td></td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone analog</td>
<td>Leuprolide</td>
<td>Prostate cancer</td>
<td></td>
</tr>
<tr>
<td>ANTIGEN AND TUMOR CELL TARGETS</td>
<td>ANTIGEN FUNCTION</td>
<td>NAKED ANTIBODIES</td>
<td>RADIOISOTOPIC-BASED ANTIBODIES</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------------</td>
<td>------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Antigen: CD20</td>
<td>Proliferation/differentiation</td>
<td>Rituximab</td>
<td>$^{131}$I-tositumomab; $^{90}$Y-ibritumomab tiuxetan</td>
</tr>
<tr>
<td>Tumor type: B-cell lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and CLL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antigen: CD52</td>
<td>Unknown</td>
<td>Alemtuzumab</td>
<td>None</td>
</tr>
<tr>
<td>Tumor type: B-cell CLL and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-cell lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antigen: CD25 α subunit</td>
<td>Activation antigen</td>
<td>Daclizumab</td>
<td>None</td>
</tr>
<tr>
<td>Tumor type: T-cell mycosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fungoides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antigen: CD33</td>
<td>Unknown</td>
<td>Gemtuzumab (humanized)</td>
<td>None</td>
</tr>
<tr>
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</tr>
<tr>
<td>Tumor type: acute myeloid leukemia</td>
<td>Tyrosine kinase</td>
<td>Trastuzumab (humanized)</td>
<td>None</td>
</tr>
<tr>
<td>Antigen: HER2/neu (ErbB-2)</td>
<td>Tyrosine kinase</td>
<td>Cetuximab (chimeric)</td>
<td>None</td>
</tr>
<tr>
<td>Tumor type: breast cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antigen: EGFR (ErbB-1)</td>
<td>Tyrosine kinase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor type: colorectal; NSCLC; pancreatic, breast</td>
<td>Angiogenesis</td>
<td>Bevacizumab (humanized)</td>
<td>None</td>
</tr>
<tr>
<td>Antigen: VEGF</td>
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<td></td>
</tr>
<tr>
<td>Tumor type: colorectal cancer</td>
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<td></td>
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</tr>
</tbody>
</table>

**Abbreviations:** CLL, chronic lymphocytic leukemia; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; VEGF, vascular-endothelial growth factor.
### Table 51-4

**Dose and Toxicity of Monoclonal Antibody-Based Drugs**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>DOSE AND SCHEDULE</th>
<th>MAJOR TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>ADCC; CDC; apoptosis</td>
<td>375 mg/m² IV infusion weekly for 4 weeks</td>
<td>Infusion-related toxicity with fever, rash, and dyspnea; B-cell depletion; late-onset neutropenia</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>ADCC; CDC; apoptosis</td>
<td>Escalation 3, 10, 30 mg/m² IV 3 times per week followed by 30 mg/m² 3 times per week for 4 to 12 weeks</td>
<td>Infusion-related toxicity, T-cell depletion with increased infection; hematopoietic suppression; pancytopenia</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>ADCC; apoptosis; inhibition of HER2 signaling with G₁ arrest</td>
<td>Loading dose of 4 mg/kg infusion followed by 2 mg/kg weekly</td>
<td>Cardiomyopathy; infusion-related toxicity</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Inhibition of EGFR signaling:</td>
<td>Loading dose of 400 mg/kg infusion</td>
<td>Infusion-related toxicity; skin rash in 75%</td>
</tr>
<tr>
<td>Drug</td>
<td>Mechanism of Action</td>
<td>Dosage/Regimen</td>
<td>Side Effects</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>-----------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bevacizumab$^{68}$</td>
<td>Inhibition of angiogenesis/neo-vascularization</td>
<td>Followed by 250 mg/kg weekly</td>
<td>Hypertension; pulmonary hemorrhage; gastrointestinal perforation; proteinuria; congestive heart failure</td>
</tr>
<tr>
<td>Denileukin diftitox$^{73}$</td>
<td>Targeted diphtheria toxin with inhibition of protein synthesis</td>
<td>9–18 μg/kg per day IV for the first 5 days every 3 weeks</td>
<td>Fever; arthralgia; asthenia; hypotension</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin$^{82}$</td>
<td>Double DNA strand breaks and apoptosis</td>
<td>2 doses of 9 mg/m² IV separated by 14 days</td>
<td>Infusion-related toxicity; hematopoietic suppression; mucosal hepatic (VOD); and skin toxicity</td>
</tr>
<tr>
<td>$^{90}$Y-ibritumomab tiuxetan$^{89}$</td>
<td>Targeted radiotherapy</td>
<td>0.4 mCi/kg IV</td>
<td>Hematologic toxicity; myelodyplasia</td>
</tr>
<tr>
<td>$^{131}$I-tositumomab$^{86}$</td>
<td>Targeted radiotherapy</td>
<td>Patient-specific dosimetry</td>
<td>Hematologic toxicity; myelodyplasia</td>
</tr>
</tbody>
</table>

*Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; EGFR, epidermal growth factor receptor; VOD, veno-occlusive disease.*
Folinic acid rescue for methotrexate toxicity

Cystitis caused by cyclophosphamide and ifosfamide can be blocked by mesna and by irrigating bladder with acetylcysteine. Both are – SH containing metabolites compounds that combined with the toxic metabolite and make them into water soluble non toxic compounds in the bladder.
- Vomiting - ondansetran
- Hyperuricemia - allopurinol
- Pulse therapy – MOPP regimen for Hodgkin’s lymphoma
- Selective exposure of tumors
- Bone marrow depression – G-CSF/GM-CSF – Sargramostim, filgrastim, pegfilgrastim
- Bleeding – platelet or granulocyte growth factors – thrombopoietin
- Bone marrow transplantation
- Thalidomide – suppress TNFα & modulate IL2
Amifostine – Amifostine (Ethyol, WH-2721) is an agent designed to produce preferential cytoprotection of normal tissues from cytotoxic therapies. The preferential cytoprotection is due to the metabolism of amifostine to the free thiol, WR-1065, the active form, by membrane-bound alkaline phosphate at normal tissue sites followed by rapid uptake into the normal tissues by facilitated diffusion. Normal tissues accumulate the free thiol, whereas uptake into neoplastic tissue is relatively slow.
The free thiol protects by covalently binding reactive anticancer drugs, such as alkylating agents, anthracyclines, and taxanes, to inactivate these agents in normal tissues. There is also evidence that amifostine can stimulate bone marrow growth in patients with marrow disorders such as the myelodysplastic syndrome and cisplatin nephrotoxicity.
NH₂-(CH₂)₃-NH-(CH₂)₂-S-PO₃H₂

Amifostine

↓

Alkaline Phosphate

NH₂-(CH₂)₃-NH-(CH₂)₂-SH

WR-1065
CANCER AS A DISEASE OF CELLS
ALKYLATING AGENTS

- Produce highly reactive carbonium ion molecules which transfer alkyl groups to cellular monomolecules by forming covalent bonds.
- The position 7 of guanine residue is specially susceptible.
- Cross linking/ abnormal pairing/ scission of DNA strands.
Cross linking of nucleic acids with protein can also take place.

Cytotoxic radiomimetic action. They act in dividing as well as resting cells.

CNS stimulants & cholinergic properties.

Metaclopramide – local vesicant only (IV)

Extravasation cause sloughing
CYCLOPHOSPHAMIDE

- Most popular anticancer drug less damaging to platelets.

- Alopecia & cystitis (ACROLEIN – toxic metabolite) (IV or IM)

- Acetylcystine bladder wash (tablets)

- Ifosfamide + mesna (SH compound that is excreted in urine. Binds & inactivates the toxic metabolite of Ifosfamide and Cyclophosphamide)

- Ifosfamide - less alopecia & less emetogenic and cause haemorrhagic cystitis.

Chloramphenicol retards the metabolism of cyclophosphamide.
USES

- Bronchogenic CA
- Breast CA
- Testicular CA
- Bladder CA
- Head & neck CA
- Osteogenic sarcoma
- Lymphoma
- Ifosfamide inj + mesna
CHLORAMBUCIL


Immuno suppressant property (tablets)

Melphalen: (tab & inj)

Multiple myeloma advanced ovarian cancer bone marrow depression is most important.

Toxicity

- Infection
- diarrhoea
- pancreatitis

Thiotepa - seldom used highly toxic(bladderCA)
BUSULFAN

- Highly specific for granulocytes precursors which are more sensitive.

Side effects:

- Hyperuricemia
- Pulmonary fibrosis
- Sterility
- Chronic myeloid leukemia (tablets)
NITROSOUREAS

- Lipid soluble alkylating agent readily crosses BBB
- Brain tumor & meningial leukemias renal damage and visceral fibrosis can occur.

Dacarbazine:
- It is different from other alkylating agents primarily inhibiting action on RNA and it is inactivated in the liver.

- Malignant melanoma, Hodgkin’s disease.

Side effects:
- Nausea and vomiting are important side effects.
ANTIMETABOLITES

- Methotrexate

- Inhibits dihydrofolate reductase (DHFR are) block the conversion of DHFA $\rightarrow$ THFA

- DHFA are enzyme is responsible for one carbon transfer reactions in denovosynthesis and amino acid inter conversions.

- Folic acid is not converted to the active coenzyme. Therefore folinic acid is used for methotrexate toxicity, which rapidly reverses the effects. Thymidine also counteracts methotrexate toxicity.
USES

- Choriocarcinoma
- To maintain remission in children with acute leukemia
- Rheumatoid arthritis
- Psoriasis
- Immunosuppressive agent

D. Methotrexate toxicity is enhanced by Salicylate, sulfonamide and dicumorol displace it from PPB.

Aspirin & sulfonamides decrease renal tubular secretion of methotrexate

Adverse effects:

- Megaloblastic anaemia and pancytopenia (tab, inj)
PURINE ANTAGONISTS

- Mercaptopurine
- Thioguanine
- Azathioprine

They are converted in the body to corresponding mononucleotides which inhibit the conversion of inosine monophosphate to adenine and guanine nucleotides. There is also feedback inhibition of de novo purine synthesis.

Useful in childhood leukemia, choriocarcinoma and also to remission in leukemia and to maintain remission 6 mercaptopurine is used.
AZOTHIOPURINE

- Marked effect in T lymphocytes.
  - Suppress CMI primarily used in
  - Organ transplantation
  - Rheumatoid arthritis.
  - Inflammatory bowel disease.

All antipurines are absorbed orally AZP and 6MP are metabolised by XO & their metabolism inhibited by allopurinol.

Dose of AZP, 6MP is reduced to 1/3 – 1/4 if allopurinol is given together.
Thioguanine is not the substrate for XO and the dose of TG should not be reduced if allopurinol is given.
PYRIMIDINE ANTAGONISTS

Fluorouracil (5 – FU)

It is converted in the body to the corresponding nucleotide 5 – fluoro – 2 – deoxyuridine MP which inhibits the conversion of DEOXYURIDILIC ACID to DEOXYTHYMIDYLIC ACID. Selective failure of DNA synthesis occurs. Thymidine partially reverses the toxicity. Resting cells are affected rapidly, multiplying cells are more susceptible.
Solid tumors:
- Breast
- Colon
- Urinary bladder
- Liver
- Topical application for cutaneous basal cell CA
- Cytarabine: It is phosphorylated in the body to corresponding nucleotide which inhibits the DNA synthesis.

The triphosphate of cytarabine inhibits DNA polymerase and blocks the generation of cytidilic acid.

USES: Remission in acute leukemia in children
Hodgkin’s disease and Non Hodgkin lymphoma
USES

Metastatic:

- ovarian & breast CA.
- Advanced head & neck CA
- Small cell lung CA
- Oesophageal adeno CA
- Hormone refractory prostate CA
- ‘stocking & glove neuropathy’ arthralgia, myalgia, mucositis and oedema.
TAXANES: Paclitaxel-It is obtained from bark of western yew tree. It enhances polymerization of tubulin. The microtubules are stabilized and depolymerization is prevented—which affect normal dynamic reorganization of microtubule network that is essential for vital interphase and mitotic functions.

Uses: Metastatic breast and ovarian carcinoma, head and neck cancer, small cell lung cancer, oesophageal adenocarcinoma and hormone refractory prostate cancer.
Docetaxel: Congener of paclitaxel
Breast & ovarian CA
S.E: Neutropenia, arrhythmias, fall in BP, heart failure are reported.

EPIPODOPHYLLOTOXINS:
Etoposide: Semisynthetic
  Podophyllotoxin
  Plant glycoside
MOA: arrest cells in G2 phase and causes DNA breaks by affecting DNA topoisomerase II
USE:
- Testicular tumors
- Lung CA
- Hodgkin’s lymphoma
- CA bladder

ADR:
- Alopecia, leucopenia and GIT disturbances.
VINCA ALKALOIDS

- These are mitotic inhibitors, bind to microtubular protein – ‘tubulin’, prevent its polymerization and assembly of microtubules, cause disruption of mitotic spindle ad interfere with cytoskeletal function. The chromosomes fail to move apart during mitosis: metaphase arrest occurs. They are cell cycle specific and act in the mitotic phase. Vincristine and vinblastine, though closely related chemically, have somewhat different spectrum of antitumour activity and toxicity.
VINCRISTINE (ONCOVIN)

- It is a rapidly acting drug, very useful for inducing remission in childhood acute leukemia, but is not good for maintenance therapy. Other indications are lymphosarcoma, Hodgkin’s disease, Wilm’s tumour, Ewing’s sarcoma and carcinoma lung. Prominent adverse effects are peripheral neuropathy and alopecia. Bone marrow depression is minimal.
VINBLASTINE

- It is primarily employed with other drugs in Hodgkin’s disease and testicular carcinoma. Bone marrow depression is more prominent while neurotoxicity and alopecia are less marked than with vincristine.
CAMPTOTHECIN ANALOGUES

Topotecan, Irinotecan is obtained from a Chinese tree.

MOA:
Interact with DNA topoisomerase I

Damage DNA

Act in S phase and arrest cell cycle at G2 phase.

Topotecan & Irinotecan – injection.

USES: Advanced colorectal carcinoma
Carcinoma of lung, cervix and ovary

ADR: Haemorrhage, thrombocytopenia
All antitumor antibiotics have antitumor activity. They intercalate between DNA strands and interfere with DNA template function.

**Actinomycin D (Dactinomycin):**
- Potent antineoplastic drug
- Efficacious in Wilm’s tumor, Rhabdomyosarcoma, Mtx resistant choriocarcinoma
Daunorubicin (Rubidomycin), Doxorubicin

USE: Solid tumors

MAO: Activate DNA topoisomerase II and generate quinone type free radical.

They have mutagenic and carcinogenic potential

ECG changes arrhythmias, hypotension, CHF, cardiomyopathy.
Mitoxantrone:
Lower cardiac toxicity
Use: In acute nonhaemolytic leukemia
Chronic myelogenous leukemia
Non Hodgkin lymphoma
CA breast
Bleomycin:

- Glycopeptide antibiotic, chelates copper and iron.
- Produce superoxide and intercalate DNA strands

USES:
- testicular tumor, squamous cell carcinoma of skin, head & neck cancer, CA oesophagous, CA genito urinary tract

S/E: pulmonary fibrosis
Mitomycin – toxic compound reserved for resistant cases of stomach, cervix, rectum bladder CA

Mithramycin: (Plicamycin)

Uses:
- Embryonal testicular tumor
- Disseminated cancer
- Bone metastasis
- Hypercalcemia

Miscellaneous drugs:

Hydroxyurea:

Ribonucleotides

Ribonucleoside diphosphate reductase

Deoxyribonucleotides

Interfere with DNA synthesis.
It depolymerizes the DNA and cause chromosomal damage
Inhibit nucleic acid synthesis
Component of mopp regimen
Used in oat cell carcinoma of lung
Weak MAO inhibitor
Alcohol cause disulfuram like reaction
L-asparaginase:
Leukemic cells are deficient in L-aspartate synthetase and depends on L-aspargin.
L-asparaginase derived from E.Coli degrades L-asparagine to L-aspartic acid and cause cancer cell death. Though remission occurs in acute leukemia in short lasting. It is used with other drugs in leukemia.
Typical anticancer symptoms are not seen
S/E: liver damage, pancreatitis, allergy and anaphylaxis
CISPLATIN

Platinum co-ordinated complex produce highly reactive compound cause cross linking of DNA (N7 guanine residue)

Also react with SH group proteins

Radiomimetic property effective in metastatic testicular and ovarian carcinoma

S/E: Highly Emetogenic, nephrotoxicity

(to reduce nephrotoxicity amifostine is used)

ototoxicity, pheripheral neuritis and shock like state on IV infusion.

Good hydration should be maintained.

Carboplatin & oxaliplatin-less toxic.
Glucocorticoids: Reduce the symptoms of Hyperurecemia, haemolysis, bleeding, intracranial tension and mediastinal edema. Has antipyretic and mood elevating action. Potentiate the antiemetic action of ondansetron and metaclopramide. Prednisolone and dexamethasone are used. Hypercorticism is a side effect. Mitotane-used in adrenal cortex CA.
Estrogens:

- Carcinoma prostate
- Androgen dependent tumour
- Male breast carcinoma
  Fosfestrol - Carcinoma of prostate
- Carcinoma breast more than 5yrs
  postmenopausal women who have been
  non responsive to tamoxifen, estrogens
  are used.

TUMOURS THAT LACK ESTROGEN RECEPTORS DO NOT RESPOND.
TAMOXIFEN:

- Pre and postmenopausal women
- Estrogen receptor positive and estrogen receptor negative tumours
- Carcinoma breast after mastectomy

Antiandrogen:

- Flutamide + GnRH analogs – used in prostate carcinoma
- Finasteride – 5-Alpha reductase inhibitor
  
  Testosterone is converted to dihydrotestosterone by 5-Alpha reductase enzyme. Used in advanced carcinoma prostate and benign enlargement of prostate.
GnRH analogs – Leuprolide, Buserelin, nafarelin used in prostate carcinoma

Progestins:

- Advanced recurrent and metastatic endometrial carcinoma and metastatic carcinoma breast
DRUG RESISTANCE

- Increase production of glutathione which inactivates the alkylating agents.
- P-glycoprotein expel the drug molecule from the site of action.
NEW DRUGS

- Pemetrexed – Antifolate used in mesothelioma
- Arsenic trioxide – chronic myeloid leukemia
- Retinoids – Tretinoin is used in prevention and treatment of cutaneous malignancy
- Imatinib – CML
- Gefitinib – epidermal growth factor inhibitor used in non small cell lung cancer
- Estramustine – estradiol + semustine – used in prostate carcinoma
Drugs used in breast carcinoma:

- Selective estrogen receptor modulator – tamoxifen & toremifene
- Selective estrogen receptor down regulator – Fulvestrant used in metastatic breast carcinoma
- Aromatase inhibitors – Androstendione is converted to testosterone by aromatase enzyme. It is inhibited by Aminoglutethimide, anastrazole, letrazole, formestane, exemestane
Monoclonal antibodies:

Trastuzumab: Recombinant DNA derived humanized monoclonal antibodies binds to HEGF receptor blocks and down regulates the receptors, antibody dependent cytotoxicity and apoptosis in malignant cells. Used in metastatic breast carcinoma.
Rituximab – used in indolent lymphoma
Alemtuzumab – used in T-cell lymphoma
Cituximab – Used in metastatic colorectal cancer
Bevacizumab – used in metastatic colorectal cancer
interferons – alpha, inhibit cell proliferation
used in hairy cell leukemia and kaposi’s sarcoma