

Dihydrofolate Reductase Inhibitors

I. Medications

A. Methotrexate

1. Breast Cancer
2. Bladder Cancer
3. Head/Neck Cancer
4. ALL
5. Crohn's
6. RA
7. Psoriasis/Psoriatic Arthritis

B. Pemetrexed

1. NSCLC

C. Pralatrexate

1. T-cell lymphoma

II. Mechanism

- A. Inhibits dihydrofolate reductase

III. Adverse Effects

- A. Stomatitis/Mucositis
- B. Myelosuppression
- C. Drug-drug interactions

Other Antimetabolites for Chemotherapy

I. 6-Mercaptopurine

A. Applications

1. ALL

B. Mechanism

1. Prodrug, inhibits purine synthesis
2. Metabolites can be inserted into DNA/RNA and render non-functional

C. Adverse Effects

1. Hepatotoxicity
2. Myelosuppression

II. 5-fluorouracil (5-FU)

A. Applications

1. Solid tumors
2. Basal cell carcinoma

B. Mechanism

1. Pyrimidine analog
2. Inhibits thymidylate synthase (produces thymidine)
3. Thymidine necessary for DNA production

C. Adverse Effects

1. Mucositis
2. Myelosuppression

III. Azacytidine

A. Applications

1. Myelodysplastic syndrome
2. AML

B. Mechanism

1. Pyrimidine analog (cytidine)
2. Activated and inserted into RNA, inhibiting RNA function

C. Adverse Effects

1. Hepatotoxicity
2. Renal Toxicity
3. Tumor-lysis syndrome
4. Myelosuppression

IV. Capecitabine

A. Applications

1. Colorectal cancer
2. Breast cancer

B. Mechanism

1. Converted to 5-FU
2. Inhibits thymidylate synthase

C. Adverse Effects

1. Mucositis
2. Myelosuppression

V. Cladribine

A. Applications

1. CLL
2. Non-Hodgkin lymphoma
3. Hairy cell leukemia

B. Mechanism

1. Activated and inserted onto 3' end of DNA, inhibiting elongation
2. Inhibits ribonucleotide reductase & inhibits DNA repair

C. Adverse Effects

1. Myelosuppression
2. Nephrotoxicity
3. Malignancy
4. Teratogenic

VI. Cytarabine

A. Applications

1. AML

B. Mechanism

1. Cytidine analog, inhibits DNA polymerase
2. Incorporates into DNA & stops chain elongation

VII. Fludarabine

A. Applications

1. CLL
2. Non-Hodgkin lymphoma
3. Hairy cell leukemia

B. Mechanism

1. Purine analog, incorporated into DNA/RNA resulting in dysfunction

C. Adverse Effects

1. Myelosuppression
2. Nephrotoxicity
3. Tumor lysis syndrome

VIII. Gemcitabine

A. Applications

1. Pancreatic cancer
2. NSCLC

B. Mechanism

1. Cytidine analog, inhibits DNA synthesis

C. Adverse Effects

1. Myelosuppression
2. Nephrotoxicity
3. Hepatotoxicity
4. Pulmonary toxicity

Anthracyclines

I. Medications

- A. Daunorubicin
- B. Doxorubicin
- C. Idarubicin
- D. Epirubicin
- E. Mitoxantrone

II. Application

- A. Leukemia
- B. Sarcoma (Doxorubicin)
- C. Breast cancer (Epirubicin)
- D. Prostate Cancer (Mitoxantrone)

III. Mechanism

- A. Produces free radicals-cytotoxic
1. Breaks DNA
2. Oxidation of DNA components
3. Peroxidation of membrane lipids

IV. Adverse Effects

- A. Cardiotoxicity

Bleomycin

I. Applications

- A. Testicular cancer
- B. Hodgkin lymphoma

II. Mechanism

- A. Nucleoside analog
 - 1. Breaks DNA via formation of superoxides & hydroxyl radicals

III. Adverse Effects

- A. Pulmonary toxicity
- B. Skin hyperpigmentation

Alkylating Agents

I. Medications

- A. Cyclophosphamide
- B. Ifosfamide
- C. Azacitidine
- D. Carmustine
- E. Lomustine
- F. Dacarbazine
- G. Temozolomide

II. Applications (varies by drug)

- A. Sarcoma
- B. Breast Cancer
- C. Non-Hodgkin lymphoma
- D. Brain tumors
- E. Melanoma

III. Mechanism

- A. Alkylates DNA, forming cross-links, which leads to programmed cell death

IV. Adverse Effects

- A. Mutagenic
- B. Cytotoxic

Vinca Alkaloids

I. Medications

- A. Vincristine
 - 1. Lymphoma
 - 2. ALL
 - 3. Wilms tumor
 - 4. Ewing sarcoma

B. Vinblastine

- 1. Lymphoma
- 2. Testicular Cancer

II. Mechanism

- A. Blocks assembly of microtubules used for cell division

III. Adverse Effects

- A. Neurotoxicity

Taxanes

I. Medications

- A. Paclitaxel
 - 1. Breast cancer
 - 2. Prostate cancer
 - 3. NSCLC

B. Docetaxel

- 1. Breast cancer
- 2. Ovarian cancer

II. Mechanism

- 1. Polymerizes & stabilizes microtubules, rendering non-functional

III. Adverse Effects

- A. Neutropenia
- B. Hypersensitivity reactions

Aromatase Inhibitors

I. Medications

- A. Anastrozole
- B. Letrozole
- C. Exemestane

II. Applications

- A. Hormone dependent breast cancer

III. Mechanism

- A. Inhibits aromatase enzyme → decreases peripheral estrogen production

IV. Adverse Effects

- A. Hot flashes

Monoclonal Antibody Cancer Therapies

I. Bevacizumab

- A. Application
 - 1. Colorectal cancer
- B. Mechanism
 - 1. Binds/inhibits VEGF
 - 2. Prevents angiogenesis

II. Cetuximab

- A. Application
 - 1. Colorectal cancer
 - 2. Head and neck cancer
- B. Mechanism
 - 1. Binds/inhibits EGFR
 - 2. Interferes with cancer cell growth

III. Rituximab

- A. Application
 - 1. RA
 - 2. Lymphoma
 - 3. CLL
- B. Mechanism
 - 1. Binds/inhibits CD20 antigen on B lymphocytes
 - 2. Induces cell mediated toxicity
- C. Adverse Effects
 - 1. Hypersensitivity reactions
 - 2. Tumor lysis syndrome

IV. Trastuzumab

- A. Applications
 - 1. Breast cancer
 - 2. Esophageal cancer
 - 3. Gastric cancer
- B. Mechanism
 - 1. Binds/inhibits HER2, effects signaling pathways
 - 2. Stimulates cytotoxicity
- C. Adverse Effects
 - 1. Congestive heart failure

Platinum-based Therapies

I. Medications

- A. Carboplatin
- B. Cisplatin
- C. Oxaliplatin

II. Applications

- 1. Solid tumors
- 2. Ovarian cancer
- 3. Bladder cancer

III. Adverse Effects

- A. Ototoxicity
- B. Nephrotoxicity
- C. Myelosuppression
- D. Hypersensitivity reactions

Topoisomerase Inhibitors

I. Medications

- A. Irinotecan
 - 1. Colorectal cancer
- B. Topotecan
 - 1. Ovarian cancer
 - 2. SCLC
- C. Etoposide
 - 1. Lung cancer
 - 2. Testicular cancer

II. Mechanism

- A. Irinotecan & Topotecan
 - 1. Inhibits topoisomerase I (DNA replication)
- B. Etoposide
 - 1. Binds topoisomerase II & DNA complex, limiting function & leaving DNA susceptible to breakage

III. Adverse Effects

- A. Myelosuppression

Tyrosine Kinase Inhibitors

I. Medications

- A. Imatinib
- B. Dasatinib
- C. Nilotinib
- D. Erlotinib
- E. Sorafenib
- F. Sunitinib

II. Applications

- A. Imatinib/Dasatinib/Nilotinib
 - 1. CML
- B. Erlotinib
 - 1. NSCLC
 - 2. Pancreatic cancer

C. Sorafenib

- 1. Renal cell carcinoma
- 2. Hepatocellular carcinoma

D. Sunitinib

- 1. Renal cell carcinoma
- 2. Pancreatic neuroendocrine tumors

III. Mechanism

- A. Inhibits tyrosine kinase enzymes in various tumor types
 - 1. Reduced cell proliferation

IV. Adverse Effects

- A. Imatinib/Dasatinib/Nilotinib
 - 1. Prolonged QT interval

Procarbazine

I. Applications

- A. Hodgkin lymphoma

II. Mechanism

- A. Cytotoxic from oxidative reactions
 - 1. Inhibits DNA/RNA/protein synthesis

III. Adverse Effects

- A. Teratogenic
- B. Neurotoxicity
- C. Monoamine oxidase inhibitor

Asparaginase

I. Applications

- A. ALL

II. Mechanism

- A. Converts asparagine to aspartic acid & ammonia
 - 1. Reduces asparagine levels, limiting growth

III. Adverse Effects

- A. Ammonia toxicity
- B. Seizures
- C. Pancreatitis
- D. Hypersensitivity reactions

Immunosuppressants

Selective Cytokine Inhibitors

I. Belatacept

A. Application

1. Kidney transplants

B. Mechanism

1. Binds CD80 & CD86 on APCs
2. Reduces T-cell stimulation & downstream effects

C. Adverse Effects

1. Post-transplant immunoproliferative disorder (Associated w/ prior EBV exposure)
2. Contraindicated in seronegative EBV pts

II. Cyclosporine

A. Application

1. Liver, kidney, heart transplants

B. Mechanism

1. Inactivates calcineurin
2. Reduces production of cytokines

C. Adverse Effects

1. Nephrotoxicity
2. Hepatotoxicity
3. Hirsutism
4. Gingival hyperplasia

III. Everolimus

A. Application

1. Kidney transplant

B. Mechanism

1. Inhibits mTOR (serine/threonine kinase)
2. Decreases T-cell proliferation

C. Adverse Effects

1. Hyperlipidemia
2. Angioedema
3. Venous & arterial thrombosis of graft

IV. Sirolimus

A. Applications

1. Kidney transplant

B. Mechanism

1. Inhibits mTOR (serine/threonine kinase)
2. Decreases T-cell proliferation

C. Adverse Effects

1. Hyperlipidemia

V. Tacrolimus

A. Applications

1. Kidney, Liver, Pancreas, Heart transplant
2. Dermatitis

B. Mechanism

1. Binds FKBP-12, reduces activation of NFATc, reducing cytokine production

C. Adverse Effects

1. Nephrotoxicity
2. Neurotoxicity

Antimetabolites for Immunosuppression

I. Azathioprine

A. Application

1. Transplant rejection

B. Mechanism

1. Inhibits purine synthesis
2. Metabolites inserted into DNA/RNA, rendering non-functional
3. Nucleotide analog

C. Adverse Effects

1. Bone marrow suppression

II. Mycophenolate

A. Application

1. Liver, kidney, heart transplants

B. Mechanism

1. Inhibits IMP dehydrogenase
2. Reduces production of GMP for nucleic acid synthesis

Anti-rejection Antibodies

I. Antithymocyte globulins

A. Application

1. Acute transplant rejection

B. Mechanism

1. Binds circulating T-cells, leading to T-cell destruction

C. Adverse Effects

1. Opportunistic infections
2. Thrombocytopenia

II. Basiliximab

A. Application

1. Acute transplant rejection

B. Mechanism

1. Binds IL-2 receptor on T-cells, limiting activation & proliferation