

CHEMOTHERAPY (15)

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General Comments:

1.

The classification of drugs as "prototype" and "secondary" drugs may be misleading, particularly with certain groups of chemotherapeutic agents such as the penicillins and cephalosporins where a number of drugs may be considered to be prototypical for different reasons (e.g., pen G, β -lactamase resistant agents, broad spectrum agents). Moreover, the medical students may confuse "prototype" with "clinically most important". Thus, it is suggested that certain "lead-in" drugs be termed "model drugs" that exemplify the mechanism of action and certain aspects of the pharmacology of a class of chemotherapeutic agents. The most important drugs from the standpoint of current clinical use should be indicated where they are distinct from the model compound.

The term "secondary drugs" should probably be reserved for agents not currently considered clinically important.

2.

The time devoted to various topics in chemotherapy will vary from institution to institution depending on a number of factors including (a) the amount of time spent in microbiology on basic mechanisms of bacterial cell wall synthesis, mechanisms of action of antibacterial drugs, etc., (b) the coverage of this class of drugs in clinical correlation conference sessions or in lectures given by clinical departments, (c) the expertise of the department, and (d) teaching time available to the department.

3.

Information regarding toxicity, antibacterial spectrum, therapeutic uses, and specific pharmacology should be covered as part of the discussion of individual drug classes. Alternatively, it could be done by clinical indications (e.g., TB, broad spectrum, etc.).

4.

Antimicrobial drugs should be organized for pedagogical reasons by mechanism of action, i.e., inhibitors of cell wall synthesis, protein synthesis inhibitors, metabolic inhibitors, DNA gyrase inhibitors, DNA damaging agents, etc.

a. Chemotherapy of Microbial Diseases

1) Introduction of chemotherapy (1 hr)

Objectives: concept of selective toxicity, concept of drug target, e.g., DNA, key enzyme steps, cell wall synthesis, protein synthesis, general mechanisms of drug resistance, rationale for drug combinations, rationale for chemoprophylaxis, appropriate and inappropriate use of antimicrobial agents, sources of information about new chemotherapeutic agents

2) Sulfonamides and DNA gyrase inhibitors (1 hr)

Objectives: historical development of antibiotics . mechanism of action, mechanism of resistance, adverse reactions, drug combinations, especially trimethoprim and sulfamethoxazole

3) Inhibitors of Cell Wall Synthesis (2 hr)

Objectives: steps of cell wall synthesis and points of attack for drugs, basic chemistry and SAR mechanisms of resistance inhibition of β -lactamases cross resistance . adverse reactions, especially allergic reactions

4) Inhibitors of protein synthesis

a) Aminoglycosides (1 hr)

Objectives: mechanisms of action; differences between drugs' mechanisms, three major types of drug toxicity: neuromuscular, vestibular oto, renal. Increased ototoxicity and nephrotoxicity in elderly., pharmacokinetics: blood levels are very important for use of this class of drugs, narrow

therapeutic index, combination chemotherapy, drug interactions

b) chloramphenicol, macrolides, and tetracyclines. (1 hr)

Objectives: mechanisms of action, antimicrobial spectrum. toxic effects with special note of hematologic effects of chloramphenicol, adverse effects on newborn, discussion of appropriate use of these agents. Their usefulness is relatively limited (except erythromycin), and they should be used only for specific therapeutic purposes.

5) Antimycobacterial Drugs (0.5 hr)

Objectives: TB as a public health problem. Atypical mycobacterial infections in AIDS and leprosy patients, mechanisms of drug action for those not covered elsewhere . appropriate use of drug combinations. toxicity pharmacogenetics of isoniazid metabolism. drug resistance

6) Antifungal Agents (1 hr)

Objectives: . mechanisms of action . topical and systemic uses

7) Antiviral Drugs (1 hr)

Objectives: . mechanisms of action, rationale for new agents. new HIV/AIDS drugs

8) Antiparasitic Drugs

Time: 2 hour

Objectives: mechanism of action of common drugs . target for anthelmintic treatment is adult non-dividing organisms . role of anchorage and motility in helminth biology and its' importance as a target for anthelmintic drugs. Malaria: disease process, life cycle of organism, importance as a world health problem. schistosomiasis: same as above . drugs of choice for most common parasitic infections of North America, e.g., trichomonas, toxoplasmosis, entamoeba, histolytica, ascariis, pinworm, hookworm, tapeworm

9) Anticancer Drugs (4 hr)

Objectives: fundamentals of cancer biology, therapeutic modalities; adjuvant chemotherapy, determinants of drug response: tumor determinants, host determinants, leukemias/lymphomas vs. solid tumors, total cell kill concept, apoptosis, selective toxicity: why it is so difficult to achieve cell cycle specificity, combination chemotherapy: rationale and examples, common and peculiar toxicities . mechanisms of drug action, pharmacokinetics, where important: e.g., methotrexate, drug resistance

10) immunomodulators (0.5 hr)

Immunosuppressives: . mechanism of action azathioprine, cyclosporine A, FK506

Note: Immunosuppressive drugs are not covered as a separate topic at represented institutions. Comments about immunosuppressive effects of anticancer drugs are made under individual agents.

Hematopoietic Growth Factors: mechanism of action
erythropoietin, rHuGM-CSF (sargramostin)

Chemotherapeutic Drugs to Consider:

Antimicrobial Agents

Cell Wall Synthesis Inhibitors:

Penicillins

Narrow spectrum Penase-sensitive

- Pen G
- PEN V

Narrow spectrum Penase-resistant (*S. aureus*)

- NAFCILLIN
- OXACILLIN
- dicloxacillin

Broad spectrum (aminopenicillins)

- AMOXICILLIN
- AMPICILLIN

Primarily antipseudomonal

- TICARCILLIN
- CARBENICILLIN

Extended spectrum

- PIPERACILLIN

Monobactams

- Aztreonam

Carbapenems

- Imipenem with cilastatin

Penicillin plus penicillinase inhibitor

- Amoxicillin plus clavulanic acid (Augmentin)
- Ticarcillin plus clavulanic acid (Timentin)

Cephalosporins

First generation

- CEPHALEXIN
- CEFAZOLIN

Second generation

- CEFOXITIN
- CEFACLOR
- CEFPROZIL

Third generation

- CEFTRIAZONE
- CEFTAZIDIME
- CEFOTAXIME

Fourth generation

- CEFEPIME

Vancomycin

Inhibitors of Protein Synthesis

Aminoglycosides

- STREPTOMYCIN
- GENTAMICIN
- TOBRAMYCIN
- AMIKACIN
- NETILMICIN

STREPTOGRAMINS

- Quinupristin
- Dalfopristin
(Synercid)

OXAZOLIDINONES

- LINEZOLID

MACROLIDES

- Erythromycin
- Clarithromycin
- Azithromycin

CHLORAMPHENICOL

ERYTHROMYCIN

CLINDAMYCIN

Tetracyclines

- TETRACYCLINE
- DOXYCYCLINE
- MINOCYCLINE

Inhibitors of DNA synthesis

Fluoroquinolones

- Norfloxacin
- Ciprofloxacin
- Levofloxacin

Sulfonamides

Best urine solubility

- SULFASOXAZOLE
- SODIUM SULFACETAMIDE
(ophthalmic use)
- SULFAMETHOXAZOLE

Topical (burns)

- SILVER SULFADIAZINE

TRIMETHOPRIM

- Use as TRIMETHOPRIM - SULFAMETHOXAZOLE combo.

Urinary Tract Antiseptics

- NITROFURANTOIN

Cationic Surfactants

- POLYMIXIN B

Drugs for Anaerobic Bacteria Only

- Metronidazole

Antimycobacterial Drugs

- ISONIAZID
- ETHAMBUTOL
- Clofazamine
- RIFAMPIN
- STREPTOMYCIN
- Rifabutin
- DAPSONE
- STREPTOMYCIN

Antifungal Drugs

Polyenes

- AMPHOTERICIN B
- NYSTATIN

Flucytosine

Imidazoles

- KETOCONAZOLE
- MICONAZOLE
- Terbinafine
- FLUCONAZOLE
- ITRACONAZOLE
- Voriconazole
- Griseofulvin

Antiviral Drugs

- AMANTADINE and Rimantadine
- ACYCLOVIR
- ZIDOVUDINE
- GANCICLOVIR
- FOSCARNET
- Interferon alpha
- Didanosine
- Valacyclovir
- Efavirenz
- Indinavir
- Lamivudine
- Zanamivir
- Ribavirin
- Lopinavir
- Nelfinavir
- Nevirapine
- Enfuvirtide
- Stavudine

Antiparasitic Drugs

Antimalarial

- CHLOROQUINE
- MEFLOQUINE
- Quinine
- PRIMAQUINE
- PYRIMETHAMINE-SULFASOXINE (Fansidar)
- atovaquone

Antiprotozoal Drugs

Amebiasis and Trichomonas

- METRONIDAZOLE
- Diloxanide
- Iodoquinol

Pneumocystis

- TRIMETHOPRIM - pentamidine
- SUFAMETHOXAZOLE
- Clindamycin plus primaquine

Toxoplasmosis

- PYRIMETHAMINE plus sulfadiazine
- Pyrimethamine plus clindamycin

Trichomonas

- METRONIDAZOLE

Antihelminthic Drugs

Flatworms

- PRAZIQUANTEL

Fluke and Tapeworm Infections

Schistosomiasis

- PRAZIQUANTEL

Filariasis

- diethylcarbamazine
- ivermectin

Intestinal Roundworms (Ascaris), Enterobius (Pinworm) and

Hookworm

- mebendazole
- pyrantel pamoate
- Albendazole

Angiostroglyliasis

- mebendazole

Trichurius (Whipworm)

Hookworm

- mebendazole
- albendazole

Trypanosomiasis

- nifurtimox or suramin
- pentamidine

Giadiosis

- metronidazole

Anticancer Drugs and Immunosuppressives

[\[Alkylating Agents\]](#) - [\[Antimetabolites\]](#) - [\[Natural Products\]](#) - [\[Antimitotics\]](#) - [\[Antimitotics\]](#) - [\[Hormones\]](#) - [\[Immunosuppressives\]](#)

Alkylating Agents

- MECHLORETHAMINE
- busulfan
- Nitrosoureas (carmustine, lomustine)
- CYCLOPHOSPHAMIDE

- procarbazine

Antimetabolites

- METHOTREXATE
- 6-MERCAPTOPYRIMIDINE
- Fludarabine
- Capecitabine

Natural Products

- dactinomycin
- DAUNORUBICIN
- DOXORUBICIN

Antimitotics

- VINCRISTINE

Miscellaneous

- HYDROXYUREA
- CISPLATIN/
Carboplatin

Hormones

- Estrogens
- Anti-estrogen
(TAMOXIFEN)

Immunosuppressives

- azathioprine
- CYCLOSPORIN A
- TACROLIMUS
(FK506)

- melphalan

- 6-THIOGUANINE
- Cytosine arabinoside

- BLEOMYCIN
- mitomycin C
- ETOPOSIDE (VP-16)

- VINBLASTINE

- asparaginase
- mitoxantrone

- PREDNISONE
- flutamide
- leuprolide

- 5-Fluorouracil
- gemcitabine

- Camptothecin
analogs: irinotecan
and topotecan

- paclitaxel/docetaxel

- amsacrine
- Imatinib

- goserelin

