Introduction to Chemotherapy

Chemotherapy now refers more broadly to the use of any chemical compound that selectively acts on microbes or cancer

effective chemotherapeutic drugs is hindered by the common legacy humans share with all living organisms
success requires exploitation of metabolic or structural differences between normal human cells and disease-producing cells.
The more closely related the undesirable cells are to normal human cells, the more difficult the task of finding a magic bullet.

For example, it is easier to cure malaria than cancer

THE PATIENT–DRUG–PATHOGEN INTERACTION

In the laboratory the strain of pathogen, the number of infecting organisms, the culture medium, the antibiotic concentration, and the duration of antibiotic exposure can be precisely specified

chemotherapy of human disease is complex, as it depends on a complex patient–drug–pathogen interaction

This interaction has six components

Pharmacokinetics: What the patient does to the drug
patient with renal failure
will have diminished renal clearance of gentamicin.

Pharmacodynamics: What the drug does to the patient

erythromycin stimulates gut motilin receptors and may induce nausea

Immunity: What the patient does to the pathogen.

For example, a patient with AIDS who is exposed to tuberculosis may develop the disease in spite of receiving a course of postexposure prophylactic antituberculosis chemotherapy, which would be effective in a patient with an intact immune system.

Sepsis: What the pathogen does to the patient.
For example, a patient with gram-negative bacillary pneumonia may receive a perfectly adequate course of antibiotic chemotherapy, only to succumb to systemic inflammatory response syndrome (SIRS), an exaggerated release of inflammatory cytokines

Resistance: What the pathogen does to the drug.

Selective toxicity: What the drug does to the pathogen.

Lethal Versus Inhibitory Effects

Antibiotics can be classified according to their effects on the biochemistry or molecular biology of pathogens

- ribosomal inhibitors (macrolides),
- cell wall disrupters (B-lactams),
- DNA disturbers (fluoroquinolones),
- metabolic poisons (trimethoprim-sulfamethoxazole).

Antibiotics also classified based on laboratory assessment of the interaction of pathogen and antibiotic drug

- static (inhibitory) or
- cidal (lethal).

Cidal effects can be a result of

- the disruption of the

cell wall or membrane when water diffuses into the high-osmolarity bacterial cytosol through the antibiotic-induced holes in the membrane, causing the bacteria to swell and burst.

- Cidal effects also

can occur as a consequence of inhibition of bacterial DNA replication or transcription.

Static effects

occur when the toxic effects of a chemotherapeutic drug are reversible.

For example, inhibition of folate synthesis interferes with methylation, an important biochemical synthetic process. Reversal of this

static effect can occur when the antibiotic concentration falls or if a compensatory increase in the synthesis of the inhibited enzymes occurs.

The static versus cidal designation is a false dichotomy

The calcification of a drug will depend on

- the pharmacological properties of the drug
- immune system function,
- inoculum size,
- Drug concentration in tissue
- duration of therapy.

A cidal drug may prove to be merely static if an inappropriately low dose or short treatment course is prescribed.

A static drug may be cidal if given in high doses for prolonged courses to exquisitely sensitive pathogens

MANAGING CHEMOTHERAPY

Physicians must select

- a drug,
- Administration route,
- dosage,
- and dosing interval.

These may be changed
several times during therapy.

the regimen is adjusted according to the results of culture and sensitivity testing.

Once a chemotherapy regimen has been selected,
the next step is to define the outcome measures

Example

Defining therapeutic success of pneumonia by

- resolution of fever
- purulent sputum production,
- normalization of the white blood cell count,
- reversal of tachypnea and hypoxia,

- Patients should be instructed to continue antibiotics for the full duration indicated, even if they feel Better
- If the patient's recovery is delayed from what is reasonably expectable, the diagnosis should be reconsidered

- Many patients receive lengthy courses of antibiotics that probably should not have been started.
- *More than half of courses of antimicrobial chemotherapy are inappropriate*

- Influenza pneumonia and viral upper respiratory infections, for example, are not controlled by antibiotics, although many patients with these illnesses receive such antibiotics.
- Of course, influenza may be complicated by post influenzal staphylococcal pneumonia, for which antibiotics are indicated.
- There should be Careful sequential evaluation of seriously ill patients who really need these antibiotics to be prescribed