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43 Introduction to Chemotherapy

Steven M. Belknap

Paul Ehrlich introduced the term *chemotherapy* in 1907 to describe his important early studies of *Trypanosoma brucei,* the tsetse fly–borne parasite that causes African trypanosomiasis (sleeping sickness). The term *chemotherapy,* initially referring to antiparasitic therapy, now refers more broadly to the use of any chemical compound that selectively acts on microbes or cancer. Ehrlich had previously developed selective chemical stains for the microscopic examination of *Mycobacterium tuberculosis* and other microorganisms, using the coal-tar derivative dyes. He tested many of these organic compounds for their selective toxicity against trypanosomes but failed to find an effective nontoxic antischistosomal agent. Turning to the chemotherapy of syphilis, Ehrlich eventually discovered the arsenical compound salvarsan, which was both remarkably nontoxic to humans and remarkably toxic against a number of treponemal diseases, including syphilis and yaws. Ehrlich called salvarsan the magic bullet.

The search for safe, effective chemotherapeutic drugs is hindered by the common evolutionary 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. Since viruses commandeer human cells to provide the necessary structural and metabolic apparatus for their functioning, they also are difficult to kill; transformed virus-infected human cells are only slightly altered normal human cells.

Humans were not the first to exploit the *selective toxicity* of chemicals. Many fungi and bacteria make toxic substances that kill or suppress the growth of competing microorganisms or facilitate infection of a host. Plants make a vast array of toxins for their self-defense. Exploitation of the selective toxicity of chemicals is an ancient and widely employed technique.

Humans first discovered this process in 1928 with Alexander Fleming's chance observation of the antibacterial effect of a substance secreted by *Penicillium notatum* mold. Howard Florey subsequently had the insight that this substance could be purified and injected into patients so as to provide systemic treatment of infection. Once scientists had learned of penicillin, they found many other naturally synthesized antibiotics, including tetracycline, streptomycin, and the cephalosporins. When the structures of these natural antibiotics were elucidated, chemists began to experiment with semisynthetic derivatives of the natural products and invented entire classes of related drugs that were safer or more effective than the naturally produced drug. The new semisynthetic or wholly synthetic drugs had improved pharmacokinetic properties, greater stability, and extended spectrums of action.

The emergence of microbial antibiotic drug resistance was speeded by the indiscriminate use of antibiotics in humans and livestock. Exposure to very low concentrations of antibiotic in meat or milk may have provided a path whereby human pathogens could eventually evolve high-level antibiotic drug resistance. Recently some strains of enterococcus and tuberculosis have developed resistance to all known antibiotic drugs. *Inappropriate use of antibiotics is very common, and it accelerates the development of resistance in pathogens.*

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. This precision cannot be obtained in patients. In addition, 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. For example, a patient with renal failure will have diminished renal clearance of gentamicin.
- *Pharmacodynamics:* What the drug does to the patient. For example, erythromycin stimulates gut motilin receptors and may induce nausea. The patient may stop taking the erythromycin.
- *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. Immunity includes both nonspecific complement-mediated opsonization and specific antibody- and cell-mediated immunity.
- *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 and counterproductive release of inflammatory cytokines.
- *Resistance:* What the pathogen does to the drug. For example, some strains of *Pseudomonas aeruginosa* produce a plasmid-mediated adenylase that inactivates gentamicin by chemically altering its structure.
- *Selective toxicity:* What the drug does to the pathogen. For example, acyclovir triphosphate, the phosphorylated derivative of acyclovir, lacks the 3′-hydroxy group necessary for adding the next nucleotide to the chain and terminates DNA elongation. This effect is selective, since herpes simplex DNA elongation is inhibited by markedly lower concentrations than is mammalian DNA elongation.

Pharmacokinetics

To be clinically useful, a chemotherapeutic drug must have both selective toxicity against pathogens and favorable pharmacokinetics. The processes of absorption, distribution, metabolism, and elimination compose a drug's pharmacokinetics. The concentration of the drug in a patient's body as a function of time is determined by the dose administered and the drug's pharmacokinetics in that patient.

Absorption from the gastrointestinal tract can be affected by other drugs and by food. Aluminum, calcium, and magnesium ions in antacids or dairy products form insoluble chelates with all tetracyclines and inhibit their absorption. Food inhibits tetracycline absorption but enhances doxycycline absorption; food delays but does not diminish metronidazole absorption; fatty food enhances griseofulvin absorption.

The chemical structure of a drug determines which enzymes metabolize it; a drug that fails to cross the cell membrane because of its polarity or size will be unmetabolized even if biochemically active degradative enzymes are present in the cytosol. Systemic use of drugs that are poorly absorbed or are destroyed by the gastrointestinal environment requires parenteral administration. Of course, if the goal is to attack pathogens in the gastrointestinal tract, then poor gastrointestinal absorption may be an advantage.

An antibiotic drug that is itself nontoxic may have metabolites that are toxic, diminishing its usefulness. For example, imipenem is hydrolyzed by renal dipeptidase to a metabolite that is inactive against bacteria but is toxic to humans. Coadministration of cilastatin inhibits the renal dipeptidase, which both prevents the formation of the toxic metabolite and decreases imipenem clearance, prolonging the half-life of the drug.

Partitioning of some drugs into cells occurs. Red blood cells parasitized by malaria selectively take up chloroquine, which accounts in part for the efficacy of this antimalarial against intracellular malarial forms. The intrahepatocellular concentration of chloroquine is 500 times that of the blood plasma concentration. Macrolides and fluoroquinolones are also selectively partitioned into cells, which accounts in part for their efficacy against mycoplasma and chlamydia, both intracellular pathogens.

Extensive protein binding of a drug decreases its free level and decreases the compound's glomerular filtration. Because protein binding is reversible, bound drug and free drug are in dynamic equilibrium; thus protein binding determines the optimal dose and dosing interval of the drug. A drug's pharmacokinetic properties are an important source of variation in the clinical response of patients to chemotherapy.

As mentioned earlier, pharmacokinetics is not solely the property of a drug but instead is the consequence of interactions between the drug and the physiology of the patient. Thus, statements like "the half-life of gentamicin is 2 hours" are not very useful, as the half-life is likely be longer or shorter in a given individual patient.

Individualization of dosing of chemotherapeutic drugs with a low therapeutic index is essential to effective, safe chemotherapy.

The concentrations of chemotherapeutic drugs in blood plasma, cerebrospinal fluid, urine, or ascites fluid can be measured to determine whether sufficient drug is present to inhibit or kill a given pathogen and to ensure that the concentration is not so high as to be toxic to the patient.

In severe bacterial infections that are difficult to eradicate, such as endocarditis or osteomyelitis, it may be important to ensure that the patient's serum remains bactericidal at the lowest, or trough, concentration in the dosing interval. Dilutions of patient's serum can be incubated with the organism isolated from the patient and the minimum bactericidal concentration determined through serial dilutions. Treatment is considered adequate if the serum remains bactericidal at a dilution of 1:8.

Pharmacodynamics

In the case of antibiotic chemotherapy, the ideal pharmacodynamic response is usually *no* pharmacodynamic response; the pharmacological target is not normal human cells but rather a parasite, a virus-infected human cell, or a cancerous cell. *The less selective the chemotherapeutic drug, the greater the severity of adverse effects.* Cancer chemotherapy is often severely toxic, even life threatening. Suppression of a viral infection, such as occurs in the treatment of HIV with antiviral drugs, is often complicated by serious drug-associated toxicity, such as hepatotoxicity or bone marrow suppression.

Compared with other pharmacological agents, antibacterial chemotherapeutic drugs are remarkably safe. Toxicity is common mainly in patients who are given inappropriately high doses or who develop high drug levels because of decreased drug clearance. Most antibiotics are renally cleared, so renal failure is a common cause of diminished antibiotic drug clearance.

The adverse reactions associated with the use of antibacterial chemotherapy include allergic reactions, toxic reactions resulting from inappropriately high drug doses, interactions with other drugs, reactions related to alterations in normal body flora, and idiosyncratic reactions. Several types of allergic responses occur, including immediate hypersensitivity reactions (hives, anaphylaxis), delayed sensitivity reactions (interstitial nephritis), and hapten-mediated serum sickness. Allergic cross-reactions to structurally related antibiotics can occur. Although an alternative non–cross-reacting antibiotic is generally preferred, desensitization protocols are available for situations in which there is no good alternative.

There is heterogeneity in human populations for the hepatic microsomal cytochrome P450 enzyme (see Chapter 4). Possession of an unfavorable phenotype may place a patient at risk for drug toxicity. For example, some patients who are slow acetylators of isoniazid may develop peripheral neuropathy with standard-dose isoniazid therapy.

Toxicity is most likely in tissues that interact with the drug. For example, gentamicin is polycationic and binds to anionic phospholipids in the cell membranes of renal proximal tubular cells, where it inhibits phospholipases and damages intracellular organelles.

Some adverse reactions are unrelated to either allergy or overdose; these are termed *idiosyncratic.* For instance, sulfonamides may precipitate acute hemolysis in some people having a glucose-6-phosphate dehydrogenase deficiency.

Many antibiotics alter the enteric microbial flora, particularly if high concentrations reach the colon. Antibiotic-sensitive bacteria are suppressed or killed, thereby removing their inhibitory effects on potentially pathogenic organisms. Overgrowth of pathogenic microbes can then occur. Unlike anaerobes, *Clostridium difficile* is resistant to clindamycin and some β-lactams. Use of such an antibiotic permits the proliferation of *C. difficile,* which then elaborates its toxin in high concentration. This toxin can cause pseudomembranous colitis, which can be fatal if not recognized and treated.

The effectiveness of chemotherapy is enhanced by adequate immune function; however, some antibiotics suppress immune function. For example, tetracyclines can decrease leukocyte chemotaxis and complement activation. Rifampin decreases the number of T lymphocytes and depresses cutaneous hypersensitivity. Antibiotics such as the sulfonamides may induce granulocytopenia or bone marrow aplasia. These effects are not well understood but may be due to enteric bacterial metabolic byproducts of these antibiotics.

Immunity

In the absence of antibiotic therapy, many patients survive infection, even infection by highly virulent pathogens. Thus, immunity may be due to factors such as a high functional reserve of organs or to an enhanced nonspecific opsonization of pathogens by complement. In other cases, specific partial immunoglobulin (Ig) G–mediated immunity was produced during prior exposure to the pathogen or a new IgM-mediated immunity develops during the course of the infection. Specific immunity can be either cell mediated or antibody mediated and may be enhanced by endogenously produced cytokines. Exogenously administered cytokines also may prove clinically useful as adjuncts to antibiotic chemotherapy.

Sepsis

Sepsis, or SIRS, is a maladaptive reaction to severe infection in which a variety of inflammatory mediators are released. Some of these mediators are bacterial

metabolic products, while others are cytokines produced by humans during infection or other inflammatory disease. These mediators can induce failure of several organ systems. Cardiac function can be suppressed; acute respiratory distress syndrome can occur; renal failure is common; and disseminated intravascular coagulation can occur.

Through their ability to cause cell lysis, antibiotics such as the β-lactams or aminoglycosides may increase the release of bacterial inflammatory mediators (e.g., gram-negative bacillary endotoxin). Antibiotics also may induce the release of endogenous cytokines, such as interleukin (IL) 1-β, IL-6, and tumor necrosis factor (TNF-α) from monocytes and IL-4 and IFN-γ from lymphocytes. These cytokines are important in inflammatory and immunological responses and may contribute to the development of SIRS. Alternatively, these cytokines also may enhance immune function and enhance antimicrobial activity. Although many drugs have been examined for their ability to reverse SIRS, no clinical studies of interventions in sepsis have yet been shown to significantly lessen mortality.

Resistance

Some pathogens are naturally resistant to certain chemotherapeutic drugs. Resistance can occur through mutation, adaptation, or gene transfer. The mechanisms accounting for innate and acquired resistance are essentially the same. Spontaneous mutation in bacterial cells occurs at a frequency of approximately one per million cells. Such mutations may confer resistance to the chemotherapeutic drug. Spontaneous mutation is not a major concern unless the use of the drug results in selection and proliferation of resistant mutant pathogens in the patient.

Resistance to an antibiotic can be the result of one or more mechanisms. Alterations in the lipopolysaccharide structure of gram-negative bacilli can affect the uptake of lipophilic drugs. Similarly, changes in porins can affect the uptake of hydrophilic drugs. Once the drug enters the cell, it may be enzymatically inactivated. Some bacteria possess pumps that remove drugs from the bacterial cytosol. The antibiotic also may be ineffective as a result of mutation of genes coding for the target site (e.g., penicillin-binding proteins, DNA gyrase, or ribosomal proteins).

It is clinically important to understand the nature of the mechanism of resistance to an antibiotic drug. For example, the β-lactam resistance of *Streptococcus pneumoniae* is due to the appearance of altered penicillin-binding proteins. Thus, the use of a combination of a β-lactam and a penicillinase inhibitor, such as clavulanate, will not overcome streptococcal β-lactam resistance, because the mechanism of resistance is not due to the production of a penicillinase.

Multiple resistance may occur. Such resistance is recognized as a major problem in controlling bacterial infections and may be either chromosome or plasmid mediated. *Plasmids* (extrachromosomal genetic elements), which code for enzymes that inactivate antimicrobials, can be transferred by conjugation and transduction from resistant bacteria to previously sensitive bacteria. Such a transfer can also occur between unrelated species of bacteria. Enzymes coded by plasmids (e.g., penicillinase, cephalosporinase, and acetylases) that are specific for a given antimicrobial inactivate the drug either by removal or addition of a chemical group from the molecule or by breaking a chemical bond. *Transposons* are segments of genetic material with insertion sequences at the end of the gene; these sequences allow genes from one organism to be easily inserted into the genetic material of another organism. Some of these transposons code for antibiotic resistance.

In vitro laboratory tests of sensitivity of a microorganism to specific antimicrobial agents are used to predict efficacy in vivo. Often, it is enough to identify the causative pathogen in culture; the general resistance pattern of the pathogen and local patterns of resistance of the pathogen may then allow proper choice of chemotherapy. It is sometimes helpful to measure the antibiotic sensitivity of the specific isolated pathogen. Generally, a battery of tests against a selection of possible antibiotic drugs is employed.

Some organisms, such as *Staphylococcus aureus, Neisseria gonorrhoeae,* and *Haemophilus influenzae,* may produce β-lactamase and therefore be resistant to penicillin and its congeners. Testing for β-lactamase production by isolates enables an early decision on the use of penicillin and congeners in treatment of the disease.

Lethal Versus Inhibitory Effects

Antibiotics can be classified according to their effects on the biochemistry or molecular biology of pathogens. There are ribosomal inhibitors (macrolides), cell wall disrupters (β-lactams), DNA disturbers (fluoroquinolones), and metabolic poisons (trimethoprim-sulfamethoxazole). Antibiotics also can be classified according to whether they are *static* (inhibitory) or *cidal* (lethal). The classification of drugs as either static or cidal is based on laboratory assessment of the interaction of pathogen and antibiotic drug.

Cidal effects can be a result of the disruption of the cell wall or membrane. Cell lysis may occur 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, inhi-

bition 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, since there is a continuous spectrum of activity between the two categories. The place of a drug along this spectrum will depend on both the pharmacological properties of the drug and such clinical factors as immune system function, inoculum size, drug concentration in tissue, and 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

Initial therapy is usually empirical; and the regimen is adjusted according to the results of culture and sensitivity testing. Physicians must select a drug, administration route, dosage, and dosing interval. These may be changed several times during therapy. For example, severe nausea and high severity of illness may necessitate initial parenteral antibiotic administration. Several days later, when the nausea has abated and the patient is clinically stable, the patient may be switched to oral chemotherapy. Such an adjustment of therapy reduces the length of hospital stay while providing effective, safe treatment.

Once a chemotherapy regimen has been selected, the next step in managing chemotherapy is to define the outcome measures that will define therapeutic success and those that will define unacceptable toxicity and necessitate discontinuation of the chosen drugs. For example, resolution of fever and purulent sputum production, normalization of the white blood cell count, reversal of tachypnea and hypoxia, and improvement of constitutional signs and symptoms may be selected as measures that will be used to evaluate whether treatment of pneumonia is successful.

Often treatment must be continued for several days after objective signs and symptoms of infection have resolved. 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 impervious to assault by antibiotics, although many patients with these illnesses receive such antibiotics. Of course, influenza may be complicated by postinfluenzal staphylococcal pneumonia, for which antibiotics *are* indicated. Careful sequential evaluation of seriously ill patients for whom antibiotics are deferred is as important as in patients for whom antibiotics are prescribed.

Study Questions

1. Choose the best answer. Selective toxicity is
(A) What the drug does to the patient
(B) What the patient does to the drug
(C) What the pathogen does to the patient
(D) What the drug does to the pathogen
(E) What the pathogen does to the drug

2. A 60-year-old patient with AIDS presents to the emergency department with a temperature of 102°F, confused, and is going in and out of consciousness. He exhibits rapid respiration and a blood pressure of 80/40. You determine that both the sputum and urine are negative by Gram staining. Which of the following is the best choice?
(A) Administer penicillin G intravenously.
(B) Administer vancomycin.
(C) Administer clindamycin and amikacin.
(D) Send a clinical sample to laboratory to find out what the organism is before treating.

3. The term magic bullet was coined for
(A) Ehrlich discovering the drug salvarsan for the treatment of syphilis
(B) Fleming discovering the antibacterial effect of penicillium notatum
(C) Florey showing the effectiveness of penicillin in patients
(D) Wilson discovering the broad spectrum antibiotic streptomycin

4. Choose the best answer for the following. The emergence of microbial antibiotic drug resistance
(A) Requires the concurrent administration of more than one antibiotic
(B) Is a direct result of the use of antibiotics in livestock
(C) Is a problem that was overcome by the development of vancomycin
(D) Is due in large part to the indiscriminate use of antibiotics in humans

5. A patient refuses to continue to take erythromycin because it makes him vomit. This is an example of which patient–drug–pathogen interaction?
   (A) Pharmacokinetics
   (B) Pharmacodynamics
   (C) Immunity
   (D) Resistance
   (E) Selective toxicity

ANSWERS

1. **D.** A drug may be selective to a particular enzyme system that is found only in the microbe and have no harmful effect on the patient. An example is sulfonamides blocking the enzyme dihydropteroate synthesis. This is a necessary step in the synthesis of dihydrofolic acid. Humans can use preformed dihydrofolic acid and do not need this enzymatic step to produce purines. Pharmacodynamics describes what the drug does to the patient. Pharmacokinetics describes what the patient does to the drug. Sepsis describes what the pathogen does to the patient. Resistance is what the pathogen does to the drug.
2. **C.** The patient is very ill, and you cannot afford to wait for the diagnosis. You administer a combination of clindamycin and amikacin to ensure that you have coverage for gram-negative and gram-positive organisms and anaerobes. Vancomycin and penicillin G are effective against Gram-positive organisms only.
3. **A.** Ehrlich called salvarsan the magic bullet for its nontoxic effect to humans and to its toxicity against the organism responsible for syphilis.
4. **D.** The indiscriminate use of antibiotics in humans is the major reason for the emergence of microbial antibiotic resistance. Such resistance, which is most apparent in hospitals, has developed to all antibiotics, including vancomycin. The use of antibiotics in livestock has compounded the problem.
5. **B.** Pharmacodynamics describes what the drug does to the patient. Erythromycin stimulates gut motilin receptors and may induce nausea; this leads to the patient refusing to continue therapy. Pharmacokinetics describes what the patient does to the drug. Immunity is what the patient does to the pathogen; resistance is what the pathogen does to the drug; and selective toxicity is what the drug does to the pathogen.

SUPPLEMENTAL READING

Lewis K et al. (eds.). Bacterial Resistance to Antimicrobials. New York: Marcel Dekker, 2001.

Levy SB. The challenge of antibiotic resistance. Sci Am 1998;278:46–53.

Nightingale Ch, Morakawa T, and Ambrose PG (eds.). Antimicrobial Pharmacodynamics in Theory and Clinical Practice. New York: Marcel Dekker, 2001.

Tufano MA et al. Antimicrobial agents induce monocytes to release IL-1 β, IL-6, and TNFα and induce lymphocytes to release IL-4 and IFN-γ Immunopharmacol Immunotoxicol 1992;14:769–782.

Rosenblatt JE. Laboratory tests used to guide antimicrobial therapy. Mayo Gin Proc 1991;66:942.

CASE Study A Beneficial Example of Pharmacokinetics

A patient is being treated with the compound imipenem for penicillin-resistant pneumococcal infection and is responding well. After several days of treatment, the patient begins vomiting and has diarrhea. You observe a slight seizure at the same time. The infection is very severe, and you do not wish to terminate the imipenem but you fear that the adverse effects will make this a necessity. What do you do?

ANSWER: You decide that a metabolite of imipenem is responsible for the sudden toxicity. You add a second drug, cilastatin, to the patient's regimen. Coadministration of cilastatin inhibits renal dipeptidase, the enzyme responsible for the metabolism of imipenem. This prevents the formation of the toxic metabolite and decreases the clearance of imipenem. The side effect disappears within 12 hours and the patient recovers from the infection.