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CHEMOTHERAPEUTIC DRUGS AND ANTINEOPLASTICS (ANTICANCER DRUGS)

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Antimicrobial Drugs are drugs which are used to treat infections. These are the agents that tend to stop the growth of microbes or kill them and then are excreted out from the body without having any effect on the human cells.

Antibiotic refers to a chemical produced by one kind of microorganism that inhibits the growth of or kills another.

Antibiotics that kill the microorganism are termed as Bactericidal

Antibiotics that inhibit the growth are termed as bacteriostatic, such that the host immune system can overcome the infection. At higher concentration some of the bacteriostatic drugs can also have a bactericidal effect.

Antimicrobials that are effective against a small group of microbes are called narrow spectrum antibiotics e.g. penicillin G

Antimicrobials that are effective against a large group of microbes are called broad spectrum antibiotics e.g. tetracycline and cephalosporin.

Mechanism of Action of Antimicrobial Drugs:

For the antimicrobial drugs to work the difference between the human cell and the bacterial cell has been exploited. These differences include:

1. Inhibition of the synthesis of cell wall. This will alter the osmotic balance of the new cells of the microbes and leave them exposed to the natural environment

making them unsuitable to live. Normally have a bactericidal effect. These drugs do not have a very toxic effect on the human cells since the human cell does not have a cell wall. E.g. vancomycin, bacitracin, penicillin, cephalosporin.

2. alter the cell membrane permeability: this alters the permeability of the material flowing in and out of the cell as a result of which the growth of the microbial agent is terminated, can be bactericidal or bacteriostatic. E.g. Nystatin

3. Inhibits protein synthesis: these exploit the process of protein synthesis by affecting the ribosome or in the nucleus by affecting the synthesis of nucleic acids. These normally have a bacteriostatic effect and can be toxic since they can also inhibit these synthesis in the human cells. E.g. tetracycline, aminoglycosides and macrolides

4. Interference with the cellular metabolism: these inhibit the synthesis of the nucleic acid by interfering with the metabolism of folic acid. In the case of bacteria they need to synthesize their own folic acid and this is done from para amino benzoic acid (PABA). These agents either interfere at the level of the PABA or take the same shape as that of PABA and inhibit the synthesis of folic acid. These normally have a bacteriostatic effect. E.g. Sulphonamides

Common Adverse effects of the antibiotics include: GI tract superinfection, hypersensitivity reaction, organ toxicity such as antibiotic associated colitis and resistance to treatment.

Why does resistance occur:

Improper and overuse of the drug

Failure to conform to appropriate dosage regime

Using broad spectrum antibiotic when the causative microbe is sensitive to a narrow spectrum one.

Residual amounts of antibiotics present in the meat that is consumed leading to resistance developed by the gut flora.

The use of a single antibiotic where a cocktail therapy would have been preferred.

Since antimicrobial drugs affect the growth of the microbial cells they can definitely be dangerous for the fetal cells and can have a teratogenic effect on them. Some of the antibiotics that do not have such an effect are: amoxycyclin, augmentin, nystatin, erythromycin and cephradine.

Antimicrobial therapy:

1. Identify the cause of infection by taking appropriate samples.
2. if cultures are taken judge the need for giving immediate therapy before the results are available
3. Consider the need of an antibiotic therapy
4. Select appropriate drug, dose and route.
5. Monitor the success of the therapy
6. asses if combination therapy needs to be given
7. Sometimes antibiotics can be used for prophylaxis as in the case of malaria.

Antibiotics:

The following antibiotics we need to know and they are:

Penicillin

Cephalosporin

Aminoglycosides

Macrolides

Tetracycline

Drugs to know:

Penicillin

Amoxycillin

Augmentin

Flucloxacillin

Cephradine

Gentamycin

Erythromycin

Tetracycline

Antibacterials that attack cell wall: belong to a group of chemically related substance known as beta – lactams. This group includes peni, cephalo and carbapenems and monobactams.

Mechanism of action:

These antibacterial are bactericidal and inhibit the formation of the rigid cell wall of the dividing bacteria. Consequences are lethal for the susceptible bacteria but relatively harmless for the human cell since we don't possess this structure.

Resistance is the main problem associated with the use of this bacteria. This occurs due to the ability of the bacteria to make beta – lactamases or penicillinases, enzymes which catalyse metabolism of and therefore inactivate these antibacterials. Another problem is the trigger of the immune system since these antibacterials are not got from a human source.

Penicillin:

Contains the β – lactum ring which inhibits the formation of the peptidoglycan bonds in the bacterial cell wall as a result of which water enters the cell by osmosis and causes the cell to burst.

The naturally derived penicillin are designated by letters. The major properties characterizing penicillin G are it is acid – labile, rapidly inactivated, erratically absorbed when taken orally and has a narrow spectrum of activity.

Other natural penicillin is penicillin V it is acid stable and has a lower potency than penicillin G.

Other penicillin are either derived synthetically or semi synthetically and hence some of their characteristics can be modified.

Longer acting penicillin: Procaine penicillin or benzathine penicillin are forms of penicillin that last in the body longer than the penicillin G. They are given IM and hence are slowly released into the circulation, since they are not as potent as the p G they are not useful against more serious infection by susceptible bacteria. It can be taken by patients who show poor compliance in taking the medicine orally.

Beta – lactamase resistant Penicillin:

Flucoxacillin, dicloxacillin.... Since these penicillins are resistant to the action of beta – lactamases an enzyme produced by some of the bacteria to inhibit the action of penicillin these can be used to treat against multiresistant staphylococcus aureus (MRSA) which produces this enzyme.

Broad spectrum Penicillin:

Amoxicillin and ampicillin these have been developed to be protective against a broad range of gram negative bacteria. However they are inactivated by beta – lactamase.

Adjuncts for greater protection against beta – lactamases.

Clavulanic acid and tazobactam have no antibacterial action but are strong inhibitors of b – lactamases.

Augmentin: amoxicillin + clavulanic acid.

Antiseptics and Antiprotozoals: From study guide.

Cephalosporins:

All drugs produced from this class are semisynthetic derivative of the antibiotic produced by the mould cephalosporium called cephalosporin C. Wider spectrum of activity over penicillin and also have longer half life. These are divided into four generation where the first generation is only active against the infections caused by staphylococci and the fourth generation are active against all bacteria that produce β – lactamases. Better coverage of gram positive bacteria and is effective in treatment against species which are resistant to aminoglycosides and other cephalosporins. Not many are available orally and have to be taken parenterally either thru IM or IV.

Polypeptide and glycopeptide antibacterial agents:

Glycopeptide such as vancomycin and polypeptide such as bacitracin also inhibit the synthesis of cell wall in the microbes but due to their toxicity are restricted to the critically ill or those clients who have demonstrated hypersensitivity towards β – lactams. They have a very narrow spectrum of activity and are effective against gram positive bacteria. Vancomycin is used in the treatment of MRSA that are resistant to other antibacterial agents. Bacitracin can also be used but it is too toxic and hence is used only topically to treat infection of the skin eye and ear.

Antibacterials that inhibit protein synthesis:

General Mechanism of action: these are products that are normally secreted from the streptomyces mould. These normally interfere with the functioning of one of the subunits of the ribosome involved in protein synthesis. The selective toxicity of these drugs arise from the structural difference between the pro and eukaryote ribosomes. Normally have a bacteriostatic action at standard therapeutic dose.

Aminoglycosides:

Prototype was streptomycin. Rarely used today. Clinically imp glycosides are framycetin, tobramycin, neomycin, gentamycin.

These act by inhibiting protein synthesis by affecting the smaller subunit of the ribosome. Normally have bactericidal properties and have a broad spectrum. These are used when the microbes are found resistant to less toxic antibacterials.

These are toxic and cause three types: nephrotoxicity, ototoxicity and neuromuscular toxicity (paralysis). These can be monitored and hence avoided. Since these are not absorbed well by the GI tract they should be given parenterally except neomycin which is given for bowel sterilization prior to surgery.

Tetracycline:

Mechanism of action: broad spectrum, bacteriostatic antibacterials. This also acts on the small subunit of the ribo. Demeclocycline is the only natural product all others are either derived semi or synthetically such as tetracycline, doxycycline and minocycline. They are effective against the plasmodium species that cause malaria.

GI disturbance and hypersensitivity reactions are the common adverse effects and superinfection when treatment is prolonged.

Tetracyclines have the ability to bind to free divalent and trivalent ions especially Ca, in the gut and blood. In the gut it results in less of the drug being absorbed. The effect of binding Ca in the blood is that less Ca is stored in the bones and teeth. Due to this reason it is not prescribed in children. Tetracyclines can cause photosensitivity reactions and hence person are advised to wear protective clothing and use sun screen.

Macrolides: Erythromycin, clarithromycin and roxithromycin. Azithromycin is closely related hence grouped with them

Mechanism of action: these affect the larger subunit of the microbial ribosomes without reacting with the human ribosome and this accounts for its relatively low human toxicity. Newer drugs have a lower potency to cause hepatotoxicity. Since they are broad spectrum they can be used as an alternative with clients showing allergy to penicillin or other related antibiotics. GI Disturbance and superinfection are common. Erythromycin is not acid stable hence needs to be enterically coated. Should be taken one hour or two before meal to ensure good absorption.

Antifungal and antiviral drugs:

Antifungal drugs are used to treat fungal infection and antiviral drugs are drugs that are used to treat against retroviruses such as HIV.

Drugs to know:

Amphotericin B

Azoles

AZT (Zidovudine)

Efavirenz

Idinavir

Nystatin

Ritonavir

Terbinafine

Antifungal drugs are used to kill or inactivate fungi and are used to treat the fungal infection these also include yeast.

There are two categories of antifungal:

1. Antibiotic antifungal (amphotericin, nystatin)
2. Synthetic antifungal agents (Azoles, terbinafine)

Details concerning antifungal drugs:

Amphotericin B: used against candida infection within the mouth and the lining of the gut. It is also used for potentially lethal fungal or yeast infection of the blood, brain, lung and bone. It is a polyene antibiotic i.e. it has many carbon carbon double bonds. It is insoluble in water and its action is enhanced against fungi with flucytosine and rifampicin. Its action is decreased with the azole drugs. It can be taken orally or parenterally, it is poorly absorbed in the GI tract and is excreted very slowly via the kidney. It has mild side effects like irritation at the site of administration, mild gastric upset. It can also cause an anaphylactic shock. If administered fast then can cause cardiac toxicity. Prolonged treatment can lead to renal toxicity, impaired liver function and anemia.

Nystatin: used in the treatment of Candida yeast infection and is also a polyene antibiotic. It is stable in dry form and has no effect on bacteria and protozoa. It can be taken orally or topically and is excreted in the faeces. Side effects is diarrhea and nausea.

Griseofulvin: Deep – seated tinea infection of nail bed, soles of feet. It is an antibiotic. It is very insoluble in water and is stable at high temperatures. It is taken orally and its absorption is dependent on the physical state of the drug and is aided by high fat food. It is excreted in the faeces. Side effects are mild and include headache, nausea, vomiting and lethargy.

Clotrimazole: is an azole and used in the treatment of candida infection or thrush of the skin, vagina or nailfolds, and tinea as well. It is too toxic for systemic use and is effective topically. Can lead to allergy, stinging, burning, itching and redness.

Miconazole: used for the same as above. It is also an azole. It can be used topically or given as IV. It has increased effects of warfarin and decreases the effect of amphotericin. Its side effects are more serious and can cause nausea, vomiting, fever, chills and IV inflammation at the site of entry.

Ketoconazole: is an azole used in the treatment of candida and histoplasmosis. Treatment can last from 1 – 6 months. It is well absorbed and widely distributed. Can be used topically or orally. Has an extensive first pass metabolism. Lead to vomiting , diarrhea, rashes and hepatotoxic.

Terbinafine: used in the treatment of fungal of skin and nail. It is an synthetic antibiotic. Increased effect with cimetidine and decreased action in the presence of anticonvulsants and rifampicin. Can be taken orally or applied topically, metabolized in the liver and excreted in the urine. Side effects are mild leading to rashes, headaches, dizziness, altered taste and drowsiness.

The Mechanism of action:

The antifungals in general work by binding to affecting the synthesis of a particular sterol called ergosterol in the fungal cell membrane. Ergosterol is not present in the human cell but it has a structure similar to cholesterol and this leads to the side effects.

1. The antibiotics bind to the ergosterol in the fungal membrane and disrupt the permeability and transport of material in and out of the cell membrane. This leads to a loss of ions and macromolecules from the fungal cell and can lead to irreversible damage.

The azoles work by inhibiting the synthesis of fungal lipids more so of ergosterol In the cell membrane. Depletion of ergosterol leads to an alteration in the fluidity of the membrane and interferes with the action of membranes associated enzymes.

Terbinafine acts by selectively inhibiting squalene epoxidase which is an enzyme involved in the synthesis of ergosterol from squalene. Accumulation of squalene within the cells is toxic.

Care consideration when using anti fungal drugs:

Monitor the lab reports for kidney and the liver.

Observe for side effects

Ensure drug compliance

Evaluate the effectiveness of the drug by noting the absence of infection

Keep the skin dry.

Ointment to be applied more than the area of infection

Corticosteroids should be avoided since they make infections worse and corticosteroid creams should be avoided since they have little effect in treating cutaneous mycoses.

Antiretroviral drugs

The genetic material of a virus is a RNA which is normally coated with either a layer of lipids or proteins. Viruses cannot replicate on their own they need the help of the reverse transcriptase which is an enzyme used for the conversion of RNA to DNA and it also needs the help of certain host enzymes to enable it to replicate. HIV is a retrovirus and this means that its genetic material is RNA and it uses RT for its replication. The principal cells that are attacked by the HIV are the hosts immune cells making the host immunosuppressed and hence making it more favorable to infection.

The antiretrovirals have the following mechanism of action:

1. Nucleoside – analogue reverse transcriptase inhibitor (NRTI)

E.g. Zidovudine, Didanosine, Zalcitabine, Lamivudine. These drugs inhibit the action of the enzyme reverse transcriptase. These drugs when taken are in the form of prodrugs and thru a number of kinase reactions they are converted into the active form. These are normally nucleoside so either thymine derivative or guanine and hence are incorporated into the viral DNA and since it is base that is not recognized by the RT its functioning is inhibited.

2. Non – nucleoside RT inhibitors (NNRTI)

These drugs bind to the RT and inhibit its action, hence the replication of the viral DNA is brought to a halt. These drugs are active when taken and are not in the prodrug form. E.g. Nevirapine, delaviridine, Efavirenz

3. Protease Inhibitor.

These drugs bind to HIV – proteases and inhibit its function as a result of which the proteins required for the virus to multiply is not available and this leads to inhibition of viral replication and maturation. E.g. Idinavir, saquinavir, ritonavir and nelfinavir.

The goal of the anti – HIV drugs is to keep the level of HIV as low as possible in the body. The best combination of the HIV drugs is not known but normally a protease inhibitor and two NRTI's are used or 1 NNRTI and 2 NRTI are used. Normally combination therapy is preferred. AZT is used for HIV positive mothers and this reduce the risk by 66% of transmission of the disease.

Common side effects:

Most of the anti – HIV drugs are metabolized in the liver hence liver toxicity is of concern. It can also lead to common side effects such as nausea, vomiting and diarrhea.

Peripheral neuropathy is common in the use of NRTI

Rashes is common to NNRTI

Lipodystrophy is common to protease inhibitors.

Compliance and drug interaction:

Since patients taking anti – HIV drugs are not only taking those drugs but are taking drugs to control the side effects and also for other conditions that they may be suffering from there are problems of compliance and drug interactions.

Protease inhibitors inhibit the action of the P450 metabolising enzyme and as a result there can be a change in the action of some other drug that is given. Some of the NNRTI's induce the enzyme P450.

Anticancer Drugs:

Covers the type of drugs used in cancer. The following is the list of the cytotoxic drugs:

Cyclophosphamide

Bleomycin

5 – Fluorouracil

Methotrexate

Vinblastine

Chemotherapy: is the use of chemical agents to destroy cancer cells. Can be used as a sole treatment or with either radiation and surgery.

There are many types of drugs that can be used in the treatment of cancer. E.g. Hormonal antagonists, interferon alfa 2a which is used to alter the hosts response to cancer and cytotoxic drugs.

A cytotoxic drug refers to a drug that damages or destroy the cells. They destroy cancer cells by inhibiting cell division. There are number of phases involved in the cell cycle where these drugs can act. They are Go, G1, S, G2 and M

The majority of the cytotoxic drugs can be divided into two categories:

These drugs are also called antineoplastic agents.

Cell – Cycle specific drugs: they act on the specific stage in the cell cycle. E.g. are plant alkaloids and antimetabolites.

Antimetabolites are active in the S phase of the cell cycle e.g. methotrexate and 5 – Fluorouracil.

Plant alkaloids are active in the M phase of the cell cycle. E.g. vinblastine.

Cell - cycle non specific drugs: these drugs act on any phase of the cell cycle. Examples of these are alkylating agents and the anti – tumour antibiotics.

Alkylating agents act on all phases of the cell cycle but are the most effective in the G1 and the S phase. The agents that are commonly used are nitrogen mustards e.g. cyclophosphamide and nitrosureas.

Anti tumour antibiotics are active in all phases of the cell cycle e.g. bleomycin, adriamycin and mitomycin – C.

Principles of Chemotherapy:

1. Most common route of administration is orally, vein and muscle. The other methods are used to increase the concentration of the drug at the tumour site.
2. The patients lab data needs to be checked before the onset of chemotherapy for e.g. blood count, platelet count, hematocrit, and renal and liver function, if there is any abnormalities then the dose needs to be adjusted or the therapy needs to be delayed.
3. Antinausea drugs and increased fluid intake is advised to overcome the side effects of the anti cancer drugs. Antiemetics are also given before and 12 – 48 hours after the therapy.
4. There are many occupational hazards that are present while dealing with cytotoxic drugs and these need to be monitored.
5. Care should be taken in the handling of these drugs since they can be degraded with heat and light.

Chemotherapy is well spaced out to reduce the tumour cells to a point where the bodies own immune system can control further growth. Normally people will receive it in 4 – 12 months of interval and this is so to provide enough time for the normal cells to heal.

What is important to note is that anticancer drug resistance can occur.

Conditions leading to resistance:

1. When the anticancer drug is used too infrequently. This is because as the tumour grows the cells undergo mutation and when the drug is used it cannot reach the cancer cells and the other cells will develop resistance to the drug.

2. Sometimes the cancerous cells can become resistant since the enzyme required to repair the damaged DNA has increased.

One way to counter this problem is to use combination therapy. Adv: lower the concentration of the drug being administered and hence decrease side effects. The drugs chosen in combination therapy will be chosen in such a way that it can affect the cell cycle in different stages, hence there is more likelihood that the DNA would not get repaired.

The basic principles of Chemotherapy:

1. The treatment should be interspersed
2. Drug combination should be used.

Side effects of anticancer drugs:

The healthy cells that are affected the most are those that undergo rapid turnover e.g. cells in the bone marrow, mucosa. Skin, hair and gonads.

Common side effects are:

Nausea, vomiting, hair loss, disturbance of the GI tract, neutropenia (low WBC count), thrombocytopenia (low platelet count) and mouth ulcers.

Things that a cancer patient should be aware of:

1. people with cold infection should take precaution when around the client since it is possible that the person is more susceptible to infection.
2. Bleeding of gums, nosebleed should be reported
3. Hydration should be maintained
4. loss of appetite is possible.
5. nausea and vomiting is possible and can be managed
6. good mouth care is imp.
7. hair loss can occur in the first and second treatment but the hair does grow back after several months of the treatment

8. Pain management is dependent on the person and whether it is chronic pain or not.