ANTICANCER DRUGS

I. Overview

It is estimated that 25 percent of the population of the United States will face a diagnosis of cancer during their lifetime, with 1.3 million new cancer patients diagnosed each year. Less than a quarter of these patients will be cured solely by surgery and/or local radiation. Most of the remainder will receive systemic chemotherapy at some time during their illness

II. Principles of Cancer Chemotherapy

Cancer chemotherapy strives to cause a lethal cytotoxic event or apoptosis in the cancer cell that can arrest a tumor's progression. The attack is generally directed toward DNA or against metabolic sites essential to cell replication ”for example, the availability of purines and pyrimidines that are the building blocks for DNA or RNA Synthesis. Ideally, these anticancer drugs should interfere only with cellular processes that are unique to malignant cells. Unfortunately, most currently available anticancer drugs do not specifically recognize neoplastic cells but, rather, affect all kinds of proliferating cells both normal and abnormal. Therefore, almost all antitumor agents have a steep dose-response curve for both toxic and therapeutic effects

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A. Treatment strategies

Goal of treatment:

- ✓ The ultimate goal of chemotherapy is a cure (that is, long-term, disease-free survival). A true cure requires the eradication of every neoplastic cell.
- ✓ If a cure is not attainable, then the goal becomes control of the disease (stop the cancer from enlarging and spreading) to extend survival and maintain the best quality of life.
- ✓ This allows the individual to maintain a normal existence, with the cancer thus being treated as a chronic disease. In either case, the neoplastic cell burden is

initially reduced (debulked), either by surgery and/or by radiation, followed by chemotherapy, immunotherapy, or a combination of these treatment modalities.

CLASSI FICATION

A. Drugs acting directly on cells (Cytotoxic drugs)

1. Alkylating agents

Nitrogen mustards: Mechlorethamine (Mustine HCl), Cyclophosphamide, Ifosfamide, Chlorambucil, Melphalan

Ethylenimine Thio-TEPA

Alkyl sulfonate Busulfan

Nitrosoureas Carmustine (BCNU), Lomustine (CCNU)

Triazine Dacarbazine (OTIC)

2. Antimetabolites**: Folate antagonist** Methotrexate (Mtx)

Purine antagonist6-Mercaptopurine (6-MP), 6-Thioguanine (6-TG), Azathioprine, Fludarabine

Pyrimidine antagonist: 5-Fluorouracil (5-FU), Cytarabine, (cytosine arabinoside)

3. Vinca alkaloids Vincristine (Oncovin), Vinblastine

4. Taxanes Paclitaxel, Docetaxel

5. Epipodophyllotoxin: Etoposide

6. Camptothecin analogues: Topotecan, Irinotecan

7. Antibiotics: Actinomycin D, (Dactinomycin), Doxorubicin, Daunorubicin (Rubidomycin)

Mitoxantrone Bleomycins, Mitomycin C

8. Miscellaneous Hydroxyurea, Procarbazine, L-Asparaginase, Cisplatin Carboplatin Imatinib

B. Drugs altering hormonal m ilieu

1 . Glucocorticoids Prednisolone and others

2. Estrogens Fosfestrol, Ethinylestradiol

3. Selective estrogen Tamoxifen,

receptor modulators Toremifene

4. Selective estrogen receptor down regulators: Fulvestrant
5. Aromatase inhibitors Letrozole, Anastrozole, Exemestane
6. Antiandrogen Flutamide, Bicalutamide
7. 5-a reductase inhibitor Finasteride, Dutasteride
8. GnRH analogues Nafarelin, Triptorelin
9. Progestins Hydroxyprogesterone acetate, etc.

ALKYLATI NG AGE NTS

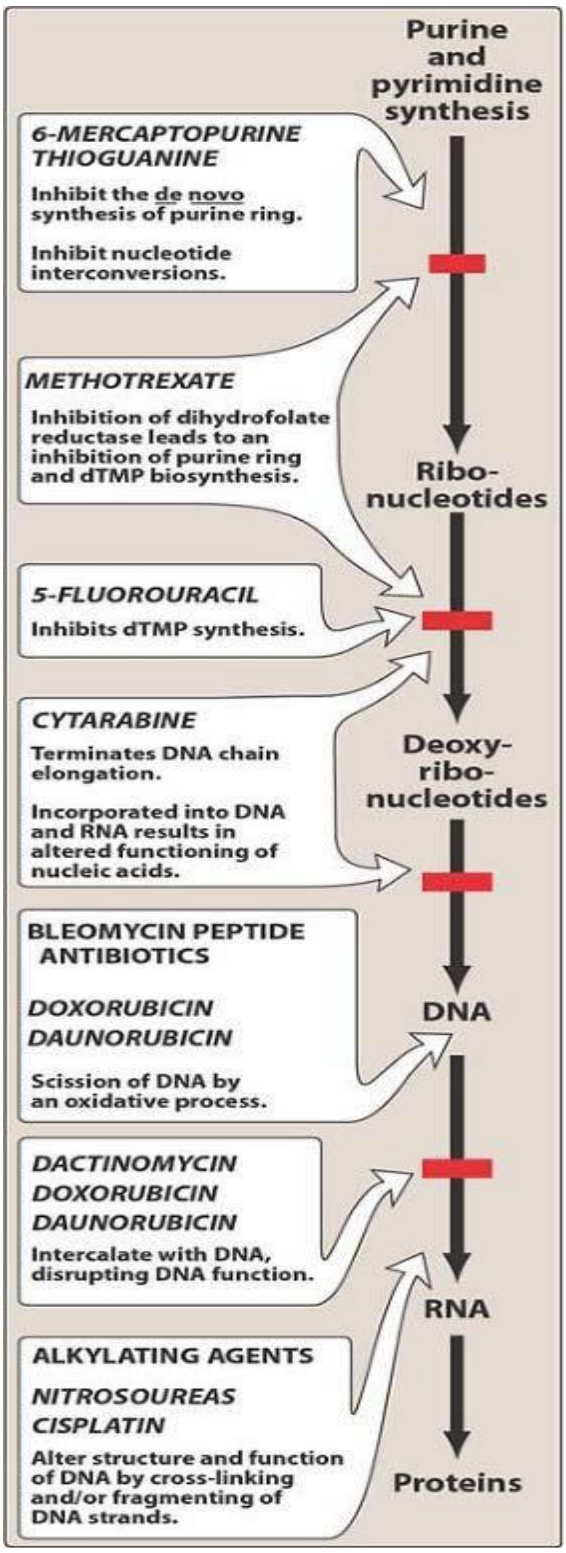
These compounds produce highly reactive carbonium ion intermediates which transfer alkyl groups to cellular macromolecules by forming covalent bonds. The position 7 of guanine residues in DNA is especially susceptible, but other molecular sites are also involved. Alkylation results in cross linking/ abnormal base pairing/ scission of DNA strand. Cross linking of nucleic (like ionizing radiation) actions.

Mechlorethamine (Mustine HCI) It is the first nitrogen mustard; highly reactive and local vesicant-c an be given only by i.v. route. It produces many acute effects like nausea, vomiting and haemodynamic changes. Extravasation during i.v. injection may cause sloughing.

ANTI MET ABO LITES

These are analogues related to normal components of DNA or of coenzymes involved in nucleic acid synthesis. They competitively inhibit utilization of the normal substrate or get themselves incorporated forming dysfunctionalmacromolecules.

1. Folate antagonist Methotrexate (Mtx) It is one of the oldest and highly efficacious antineoplastic drugs**; inhibits dihydrofolate reductase (DHFRase)-blocking the conversion of dihydrofolic acid (DHFA) to tetrahydrofolic acid (THFA)** which is an essential coenzyme required for one carbon transfer reactions in de novo purine synthesis and amino acid interconversions. Methotrexate has cell cycle specific actionkills cells in S phase; primarily inhibits DNA synthesis, but also affects RNA and protein synthesis. It exerts major toxicity on bone marrow-low doses given repeatedly cause megaloblastic anaemia, but high doses produce pancytopenia. Desquamation and bleeding may occur in g.i.t.



2. Purine antagonists

Mercaptopurine (6-MP) and thioguanine (6-TG) These are highly effective antineoplastic drugs. They are converted in the body to the corresponding monoribonucleotides ***which inhibit the conversion of inosine monophosphate to adenine and guanine nucleotides.***

There is also feedbackinhibition of de novo purine synthesis. They are especially useful in childhood acute leukaemia, choriocarcinoma and have been employed in some solid tumours as well. In acute leukaemia, both have been used in combination regimens to induce remission and 6-MP to maintain it as well.

Pyrimidine antagonists: Pyrimidine analogues have varied applications as antineoplastic,antifungal and antipsoriatic agents.

Fluorouracil U, -FU) is converted in the body to the corresponding nucleotide 5-fluoro-2- deoxyuridine monophosphate, ***which inhibits thymidylate synthase and blocks the conversion of deoxyuridilic acid to deoxythymidylic acid***. Selective failure of DNA synthesisoccurs due to non-availability of thymidylate: thymidine can partially reverse its toxicity. Fluorouracil itself gets incorporated into nucleic acids and this may contribute to its toxicity. Even resting cells are affected, though rapidly multiplying ones are more susceptible.

VINCA ALKALOIDS

These *are mitotic inhibitors, bind to microtubular protein-'tubulin', prevent its polymerization and assembly of microtubules, cause disruption of mitotic spindle and interfere with cytoskeletal function.* The chromosomes fail to move apart during mitosis: metaphase arrest occurs. They are cell cycle specific and act in the mitotic phase. Vincristine and vinblastine, though closely related chemically, have somewhat different spectrum of antitumour activity and toxicity.

Vincristine (oncovin) It is a rapidly acting drug, very useful for inducing remission in childhood acute leukaemia, but is not good for maintenance therapy. Other indications are lymphosarcoma, Hodgkin's disease, Wilms' tumour, Ewing's sarcoma and carcinoma lung. Prominent adverse effects are peripheral neuropathy and alopecia. Bone marrow depression isminimal.

TAXANES

Paclitaxel It is a complex diterpin taxane obtained from bark of the Western yew tree, which exerts cytotoxic action by a novel mechanism. It enhances polymerization of

tubulin: a mechanism opposite to that of vinca alkaloids. The microtubules are stabilized and their depolymerization is prevented. This stability results in inhibition of normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic functions. Abnormal arrays or 'bundles' of microtubules are produced throughout thecell cycle.