Lecture 11+12 - Anticancer Drugs

Treatment of cancer includes
1-cytotoxic drugs
2-isotopes which emit B-radiation that destroy cancer cells, e.g I_{131},P_{32}, Au_{193}
3-hormones
4-immunotherapy
Principles of cancer chemotherapy
1-objective of cancer treatment
a) Radical cure: no recurrence of cancer but this is rarely obtained if not obtained then:
b) Palliation "alleviation of symptoms" life prolongation with disappearance of tumor but recurrence is and even present possibility
2- Indication of treatment:
a) When neoplasm are disseminated and not available to surgery
b) As supplement to surgery and radiation to attack micrometastasis (this is called adjuvant chemotherapy) e.g breast cancer

cytotoxic drugs:

there drugs act against all multiplying cells, B.M, mucosal surface (gut), hair follicle, RES and germ cells are rapidly dividing, thus they are targets for cytotoxic drugs (side effect)
Growth rate of most tumors is initially rapid but decrease as tumor size decrease, thus decrease tumor burden through surgery and radiation promotes recruitment of the remaining cells into active proliferation and increase susceptibility to cytotoxic drugs.

Treatment protocols:
Combination chemotherapy is always more effective than single drug, cytotoxic with qualitatively different toxicities and different mechanism of action are usually combined at full doses with least side effects.
This will lead to increase responses rates and decrease chances of resistance when we use drugs with similar dose-limiting toxicities, the dose of each must be decreased.

Problems of chemotherapy:
1-resistance:
a) Inherited resistance: some neoplastic cells are inherently resistant e.g melanoma cells
b) Acquired resistance: developed after prolong administration of low drug dose (single drug used) this can be decrease by using combination drug therapy
c)multiple resistance: a major problem now, which is due to activation of ATP dependant membrane, efflux pump acting via protein called (P-glycoprotein) which pump the drug out of the cell
cytotoxic differ in capacity to stimulate (p-glycoprotein) and same as cisaplatin doesn't include this type of resistance
2-toxicity: therapy aimed at killing proliferation cells also effects normal cell undergoing rapid proliferation, e.g bone marrow, RES, GI mucosa, hair cells
1- bone marrow and RES: pancytopenia and immune suppression (humeral and cellular immunity) that will lead to opportunistic infection so bone marrow depression is the most important limiting factor in using these drugs

2-GIt gut epi and other mucosal surfaces: damage to rapidly dividing epi lead to mucositis which include:
Stomatitis and mouth ulcer, vomiting and diarrhea
3-skin: hair follicle leads to alopecia , recover after 2-6 months of stopping therapy but it may re-grow with different color.
Delayed wornd healing.
Local toxicity if extravasation occurred (all of the above side effects are reversible)
4- Gonads (germs cells + reproduction)
Sterility, mutagenesis, teratogensis and abortion
5- kidney: hyperuricemia, gouty nephropathy due to release of nucleoprotein from destruction of large number of tumor cells which leads to increased uric acid
Treatment of fluid alkalinization of urine, allupurinol.
Lytic syndrome: a syndrome in which we have cells that are stucked in kidney and leads to tubular necrosis

3-ocogenic effects

Non lymphoblastic leukemia as lymphoma after many years of treatment with alkylating agents
Specific toxicity (irreversible organ damage)
Hepattoxicity-6MP
Cardiac toxicity-daunorubicin
Nephrotoxicity- vincristine
Lung toxicity-busulfan
Bladder toxicity-cyclophosphamide
Vomiting, stomatitis, alopecia more or less with all neoplastic agents. The duration o f side effects may be transient as alopecia

Contraindication:

1-very advancer disease and debilated patients
2-active infection as T.B leads to decreased immunity to therapy and increased infection
3-pre-existing B.M depression as in anemia .

Classes of cytotoxic drugs

1-alkylating agents
2-spindle poisons: microtubule inhibitors" or plant alkaloids
3-antibiotics
4-antimetabolites
5-miscellaneous

Alkylating agents (cycle non-specific)

Mechanism of action: they react strongly with nucleophilic substances and form a covalent linkage. Their toxic effects are due to free radicals formation and alkylation of component of DNA, RNA and cellular proteins
These reactions have profound effect on DNA replication and transaction and may cause mutagenesis and carcinogenesis
e.g. nitrogen mustards and ethylenimines act by transferring alkyl group to DNA strands breaking or cross-linking of the 2 strands so that normal synthesis will be prevented

MOPP

Other members:

1-mustine (mechlorethamine)

Used primarily for Hodgkin's lymphoma as a part pf the MOPP it is used also in some solid tumors.

Powerful blistening agent given only I.V and it is very unstable in solution

2-cyclophosphamide and ifosfamide

Very closely related to mustard agents that share most of the same toxicity they are unique in that:

a) can be taken orally

b)they have to be transformed in to hydroxylated intermediates by cytochrome P450 to become cytotoxic and the hydroxylated form undergoes breakdown to form active compounds (phosphoramid mustard and acrolein) which leads to the reaction of phosphoramid with DNA is considered to be cytotoxic step.

Acrolein responsible for hemorrhagic cystitis

Uses:

1-neoplastic conditions: part pf a regimen for wide variety of neoplasm as Hodgkin's disease, lymphoma, chronic lymphoid leukemia, meyloma, breast cancer and lung cancer

2-non-neoplastic

Rheumatoid arthritis because it is one of the immunosuppressive drugs, nephritic syndrome

Side effects:

GIT side effects, alopecia, B.B depression, infertility, hemorrhage cystitis leads to fibrosis of the bladder due to certain acrolein toxicity incase of cyclopphopharmide, the latter is treated by hydration and MESNA (sodium 2-mercaptoethane sulfonate) which inactivate the toxic compound

These drugs are preferentially given orally and some amount of parent drug is excreted in urine and feces

3-nitrosoureases: they include

a-carmustine and lamustine "closely related"

b-streptozocin: specifically toxic to B-cell of the pancreas, so used in inulinoma, it cause diabetes and reversible renal damage

4-platinum analogues

Cisplatin is more toxic, carboplatin is less toxic

Excreted by kidney

Spindle poison (plant alkaloids)

Mitotic spindle consist of chromatin and a system of microtubules composed of protein tubulin, its essential for the internal movement occurring in the cytoplasm of all eukaryotic cells and for equal positioning og DNa into 2 daughter cells formed when the cell divides

Plant alkaloids cause cytotoxicity by disrupting this process by effecting the equilibrium between polymerized and de-polymerized forms of microtubules (black mitosis)

Plant alkaloids include:

1-vinca alkaloids:vincristine, vinblastine, navelbine

2-toxoid: paditaxal "teraxal", docetaxal

3-podpphyllotoxins: etoposide "VP-16"

Antibiotics for cancer therapy

They are natural substances that inhibit DNA and RNA synthesis, they vehave both as phase-specific (bleomycin) and non-phase specific, they include
Dactinomycin, idurubicin, epirubicin, doxorubicin, aclarubicin, daunorubicin, plicamycin, bleomycin, amsacrine, mitroxantron, mitomycin

Dactinomycin (actinomycin D)

Mechanism of action:
It intercalates between guanine-cytosine base pairs of DNa forming a stable (drug DNa complex) and at high doses it may inhibit DNa synthesis and may cause strands break

Doxorubicin (adriamycin) and daunorubicin (danomycin)

Classified as anthracycline antibiotics, doxorubicin is the hydroxylated form of daunorubicin
Site of action (mechanism of action)
1-intercalation with DNA the drug inserts non-specifically between pairs causing local uncoiling and blocking of DNA and RNA synthesis
2-binding to cell membrane altering function of transport process coupled to phosphatidyl inositol activation (IP3)
3-generation of O2 radicals (formation of O2 and H2O2) causing single strand breaks in DNA

Tissue with adequate superoxide dismutase (it activates O2) and glutathione peroxidase are protected while tissue having low dismutase or oxidase are more liable for injury
Heart and tumor cells lack these enzyme (which are responsible for removing O2 and O2 radicals) they resemble tumor cell in that concept thus these drugs will effect heart cells as well as tumor cells leading to cardiac toxicity (cardio-myopathy)

Bleomycin

Cucle-specific causes cells to accumulate in G2 phase, it causes scission of DNa by an oxidation process by forming O2 and OH radicals
Side effects:
1-pulmonary toxicity lead to fatal pulmonary fibrosis
2-hypertophic skin changes: hyperpigmentation of hands and nails and alopecia
3-high incidence of fever and chills
4-B.M depression (rare and mild)

Plicamycin (mithramycin)

Act through restriction of DNA-directed RNA synthesis, it has specific toxicity to osteoclast preventing their resorping it thus decrease ca concentration.
In hypercalcemia especially in those with bone tumors

Antimetabolites

Are phase specific act during S-phase of cell cycle
Are structurally related to normal cellular component they generally interfere with availability of normal purine and pyrimidine, nucleotides precursors by inhibiting their synthesis or by competing g with them in DNA or RNA synthesis
These are:
1-folic acid antagonist: methotrexate MTX
2-purine antagonist: mercaptopurine 6-MP, azathiopurine and thiogaunine
3-pyrimidine antagonist: cyterabine (arabinoside), fluorouracil (5-Fu), fludorabine

Methotrexate

Mechanism of action: structurally related to folic acid, it acts as folic acid antagonist by inhibiting (dihydrofolate reductase) which is responsible for conversion of folic acid into active form (tetrahydrofolic acid) which is important in synthesis amino acid and nucleic acid.

Methotrexate enters cells by active transport process, it has strong affinity to FH2 reducatase this inhibitory step by MTX can be passed by giving folonic acid (leucovorin) and this is called leucovorin rescue which means B.M rescue
Kinetics:

1- rapidly absorbed from gut
2- given I.M, I.V, intrathecally because it poorly penetrate CSF
3- its metabolized inside the cells to polyglutamate derivatives, they inhibit FH@ reducatse and remacin in cells even in the absence on the extra cellular drug (i.e. the effect of MTX lasts for time after it has been given)
4- MTX also undergoes hydroxylation (7-OH metabolites) both (MTX+metabolite) are excreted in urine
5- 7-OH metabolite has decrease water solubility which leads to crystal urea, therefore good hydration alkylinization of urine is important to avoid renal toxicity

Contraindication:
Most important is pregnancy because it causes abortion and teratogenicity (infact MTX may be combined with PG to induce abortion)

Mercaptopurine

It's a thiol analogue of hypoxanthine
Azathioprine is effective after conversion to 6-MP

Azathioprine (immuran)

1-widely used immunosuppressive agent
2-given with steroids incase of renal transplantation
3-act as steroid-sparing agent in crohn's disease
Mechanism of action:
It penetrates the target cells and converted to the corresponding nucleotide (6-MP ribose phosphate) also know as (thio-IMP) or called (6-thioinosinic a) this process is catalyzed by hypoxanthine guanine phosphoribosyl transferase (HGPRT)
Thio-IMP can feed back to inhibit the 1st step of de-novo purine synthesis
In addition, there will be dysfunction of DNA and RNA resulting from incorporation of guanylate analogues generated from unnatural nucleotide

6-thioguanine (6-TG)

Purine analogue used for treatrement of acute non-lymphoncytic leukemia in combination with dauno-rubicine and cytarabin
Like 6-MP it must be converted to the corresponding nucleotide from will inhibit purine synthesis
6-TG can be incorporated in DNA and RNA
Very little is metabolized to thiouric acid, therefore allopurinol doesn't doesn't potentiate 6-TG toxicity

Side effect same as 6-MP

5-Fluorouracile (5-FU)

A pyrimidine analogue to be cytotoxic it's converted to the corresponding deoxynucleotide
(5-F dump) which competes with dump for thy midylate synthestase (T.S)
Here folic acid when given it will lead to increase in the cytotoxic effect of the drug because rate of reaction will increase.

Cytarabin (Ara-C)

Pyrimide analogue
Must be converted to corresponding nucleotide (Ara-CTP) to be cytotoxic also incorporated into DNA and can be terminate chain elongation
It is S-phase specific

Miscellaneous

Procarbazine
Inhibit DNA, RNA synthesis
It is part of MOPP synthesis for Hodgkin's disease
Given orally and parenterally
Penetrate CSF and excreted into urine together with its metabolite

Asparginase
Derived from bacteria, it catalyse deamination of aspargine cell require acid and ammonia
Neoplastic cell require extrasource of aspargine to support growth and function
The drug will hydrolyze blood aspargine so deprives tumor cells from this nutrient required for protein synthesis