دفعة يقين 2025

HLS

PHARMACOLOGY فارما

LECTURE المحاضرة

8

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EDITED تعديل

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#معكم_خطوة_بخطوة

HLS Pharmacology lecture "8"

Induction Immunosuppressive Therapy

- usually performed with very powerful , effective and potent immunosuppression (more than drugs that maintainimmunosuppression).
- they are given before the organ transplantation operation.
- most of them are either monoclonal or polyclonal antibody.

during T-cell activation (step 3), it binds with cytokinase mainly IL-2 resulting in :
-activate mTOR derivatives proliferation and growth (increase thier number)
- proteins that are transcripted by mTOR pathway(like ILs) will increase..

suffix for monoclonal antibody

Basiliximab

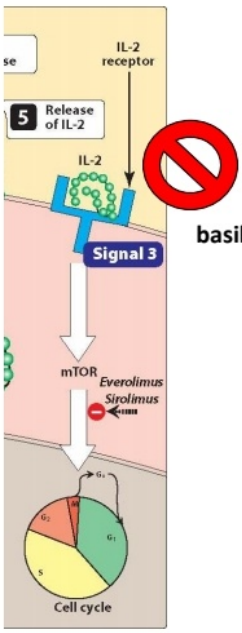
- Chimeric/monoclonal antibody
- **Effect:** prevents T-cell proliferation
- **Mechanism of action:** binds to and blocks IL-2 receptors on activated T-cells

PREVENTS PROLIFERATION BUT NOT T-CELL DEPLETING
-the drug doesn't kill T-cells
- other anti-proliferative therapy kill T-cells

- **Uses:**

1. Prevention of acute rejection in renal transplantation.
2. Delays the use of calcineurin inhibitors.

it is beneficial, because calcineurin inhibitors are nephrotoxic.

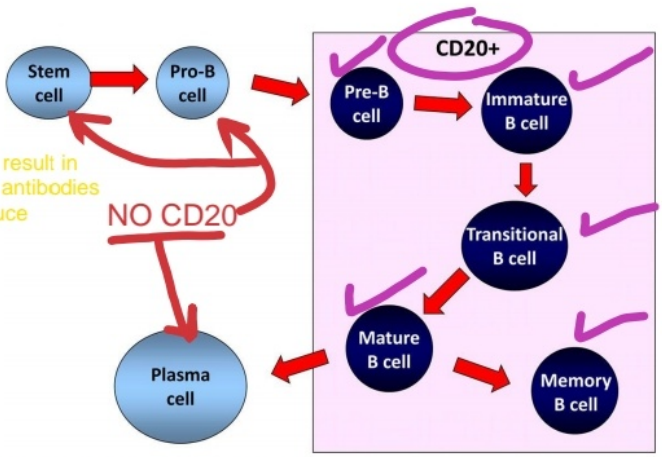


this drug is special, because it's working on B-cell not T-cell.
* B-cell could be activated and differentiated into memory cell (circulates in blood and responsiblefor long life immunity) and plasma cell (last phaseofB-cellmaturation responsibleforproductionofantibodyand heomoral immunity.)

Rituximab

- Chimeric, monoclonal
- **Target**: CD20 on pre-B cells, mature B cells and memory B cells
- **Effects**:
  1. B-cell depletion (B-cell lysis)
  2. Blocks B-cell activation
  3. Prevents B-cell maturation to antibody-forming plasma cells

by this , the cell will die and result in absence of plasma cells and antibodies and by this immunity will reduce

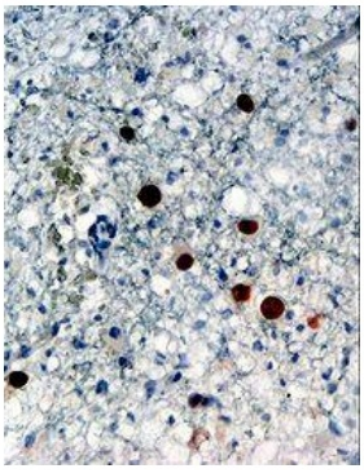


* depending on, rituximab can't work on plasma cell, because it has no CD20 to work on.
- rituximab can be used in case of B-cell leukaemia, but can't be used in case of multiple myloma which refer to plasma cell.

Rituximab

autoimmune dz

- **Indications**: rheumatoid arthritis, posttransplant lymphoproliferative disease (PTLD), B-cell lymphoma
- **Adverse effects**: black-boxed for reactivation of JC virus → leading to Progressive Multifocal Leukoencephalopathy (PML) life threatening



JC virus is an opportunistic virus which usually becomes activate in immunosuppression individual either it is acquired (like AIDS pts) or genatic.

Rituxan
rituximab

Black Box Warnings

Infusion Rxns
serious, incl. fatal infusion rxns can occur; deaths reported w/in 24h of infusion; approx. 80% fatal infusion rxns occur w/ 1st infusion; monitor pts closely; D/C tx and treat severe infusion rxns

Severe Mucocutaneous Rxns
can occur, incl. fatal rxns

HBV Reactivation
can occur, incl. cases resulting in fulminant hepatitis, hepatic failure, and death; screen all pts for HBV infection before initial tx; monitor for s/sx HBV reactivation during tx and after D/C; D/C rituximab and concomitant drugs if HBV reactivation occurs

Progressive Multifocal Leukoencephalopathy
can occur, incl. fatal PML

Bortezomib

proteasome helps in surviving B-cells and T-cells.

- Proteasome inhibitor
- **Effects**:
  1. Apoptosis of plasma cells
  2. Decreases antibody production
- **Indications**: multiple myeloma, antibody-mediated rejection in transplant patients

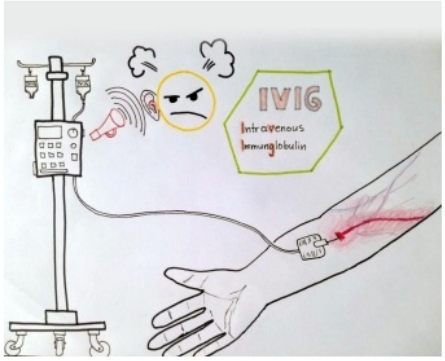
it isn't a single drug it is a mixture of immunoglobulins which is the main protein that produces antibodies.

Intravenous Immunoglobulin (IVIG)

- Immunoglobulins derived from human plasma (donors)
- **Effect:** immunomodulation, B-cell apoptosis
  with uncleared mechanism
- **Indications:**

1. Autoimmune diseases
2. Pretransplant desensitization
3. Antibody-mediated rejection

- **Adverse effects:** headache, fever, chills, hypotension/hypertension and hypersensitivity



Chemotherapy for Hematological Malignancies

Pharmacology and Toxicology
HLS Module
Second Year Medical Students
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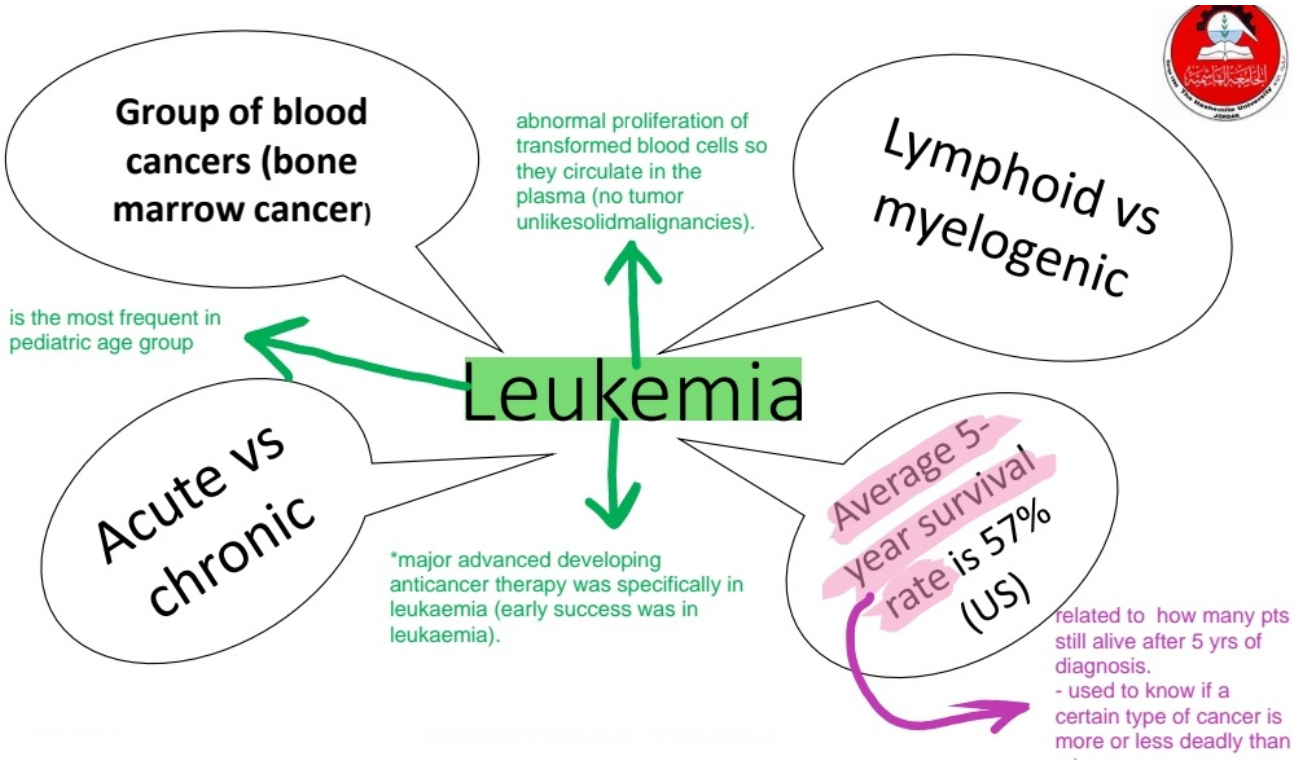
cancers of the blood like leukaemia , lymphoma and other which called " liquid malignancies" . solid malignancies like brain cancer and breast cancer.



Phases of Drug Treatment of Acute Lymphoblastic Leukemia

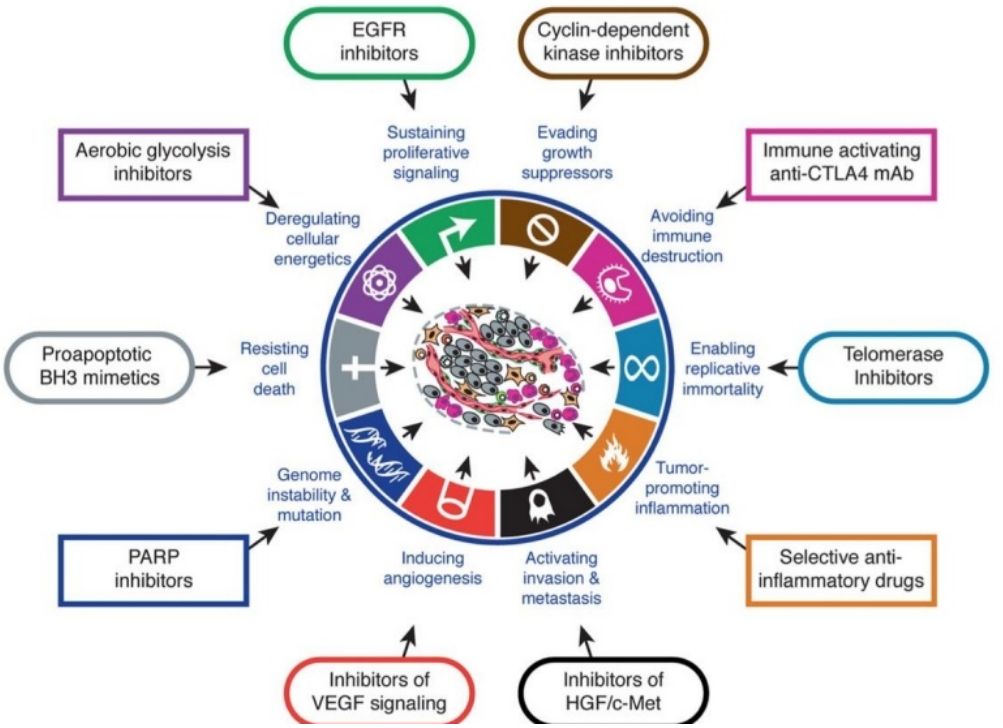
we can deal with most cancers by surgical restricted , but it cannot be applied in leukaemia because it doesn't contain a tumour , leukaemia is treated mainly by chemotherapy.
reach arond 99.9% free leukaemic cells as possible as we can.

1) **Induction**
- destroys the leukemia cells to achieve remission
- ~ 95% of children with ALL enter remission after 1 month of induction treatment

2) **Consolidation**
- further reduces the number of leukemia cells
- prevents the remaining leukemia cells from developing resistance

3) **Maintenance**
- to prevent recurrence

- **Central Nervous System (CNS) prophylaxis** against CNS leukaemia



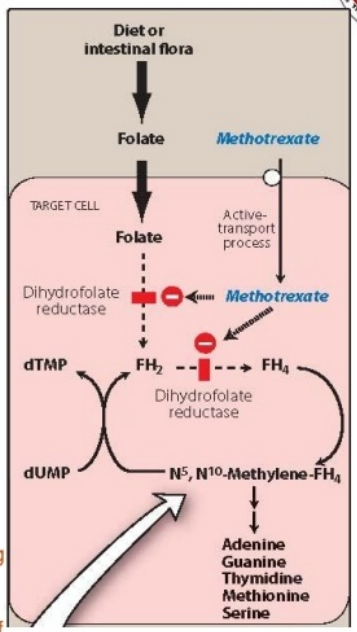
Antimetabolites

folic acid is so important as a cofactor (vitamine) in purine and peramedine synthesis, and in order to be active , folic acid should be in reduced form (tetrahydrofolate).

by inhibition of folic acid , the work of folic acid will stop , so purine and peramedine will reduced in number which will result on inhibition the synthesis of DNA and by this , the proliferation of tumour cells will be prevented.

Methotrexate

and other drugs that derived from it like anti-folate.



- *Methotrexate* is structurally related to folic acid
- **Mechanism of action:** INHIBITS MAMMALIAN DIHYDROFOLATE REDUCTASE (DHFR)
- **Cell cycle specific:** S phase

because it contains DNA replication and synthesis

dihydrofolate reductase enzyme is the target of other drugs depending on species, for example: - in mammalian this enzyme is the target of methotrexate.

- in bacteria, this enzyme is the target of trimethodrain (stop growth of bacteria).

Remember....

6-Mercaptopurine

interfer with the metabolism of purine so that they can be used to treat cancer.

- Remember from immunosuppressants
- Used as *maintenance therapy* in acute lymphoblastic leukemia

cell cycle specific in S-phase.

Cytarabine (cytosine arabinoside, ara-C)

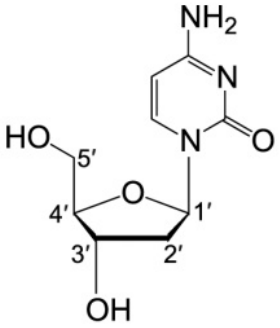
- Analogue of 2'-deoxycytidine
- **Mechanism of action:**

➢ pyrimidine antagonist

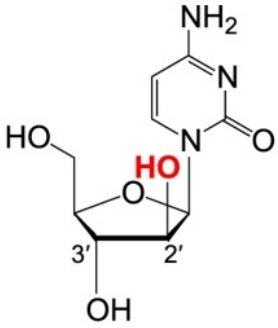
➢ Inhibitor of DNA polymerase

➢ If incorporated into DNA → terminates chain elongation

➢ *Must be phosphorylated by deoxycytidine kinase to the nucleotide form*



2'-Deoxycytidine, dC



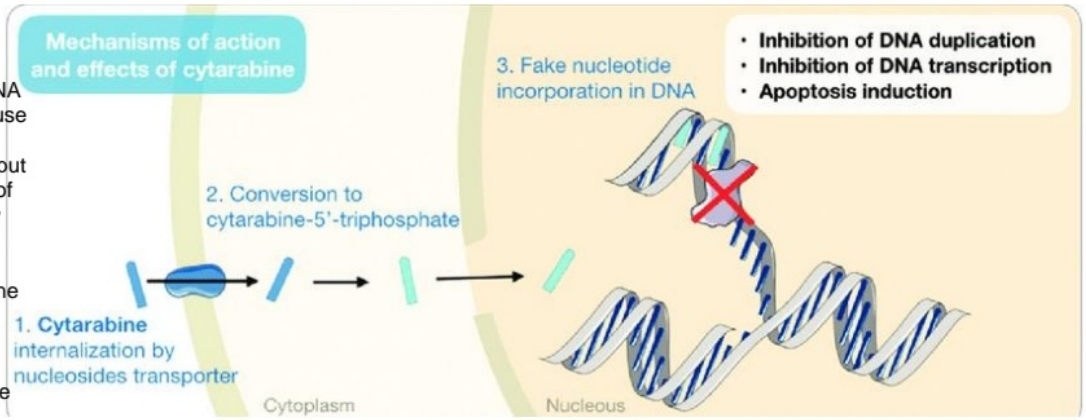
Cytarabine, AraC

cytarabine circulates in blood and then enter to the cancer cell by normal nucleotide transformers (because of similarity in structure) then it be phosphorylated in cytoplasm by deoxycytatabine kinase and converted into triphosphate , DNA polymerase will use it as normal nucleotides and put it in new srands of DNA ,so the new DNA will not be completed.
by this , cytarabine inhibits DNA transcription and doublication and stop growth of the cell then death.

Cytarabine (cytosine arabinoside, ara-C)

Is cytarabine cell cycle-specific?

Would cytarabine be effective orally?



Cytarabine (cytosine arabinoside, ara-C)

- **Therapeutic uses:**
  1. Acute myelogenous leukemia
  2. Meningeal Leukemia
  3. Refractory Leukemia
  4. etc.... like CNS leukaemia

- **Adverse effects**
  - ☐N/V/D
  - ☐Myelosuppression
  - ☐Hepatotoxicity
  - ☐Neurotoxicity

THE END

BEST WISHES 😊😊🌹🌹