# Anticancer drugs

**Anticancer drugs** are agents that inhibit proliferation or irreversibly damage tumor cells.

Treatment of malignant tumors with anticancer agents is denoted by the term "chemotherapy".

## Purposes of the chemotherapy

1. To Heal - long-term, relapse-free survival (with chorionepithelioma of the uterus, testicular seminoma, acute lymphatic leukemia in children and some others).
2. To Improve the quality of life of the patient (for ovarian cancer and the body of the uterus, breast cancer, lymphosarcoma, lymphogranulomatosis, etc.).
3. Palliative goal - relief of symptoms, reduction of toxicity in the IV stage of the disease.

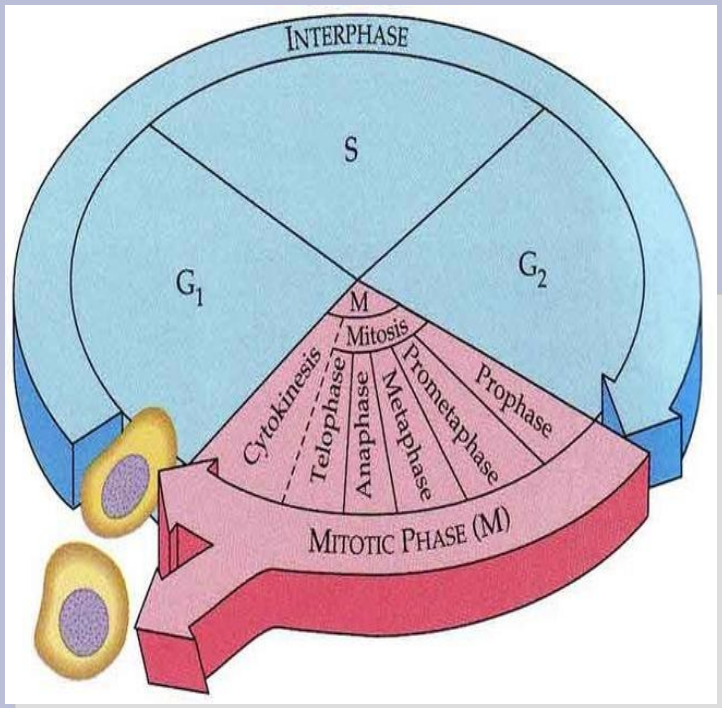
## Objectives of chemotherapy.

**4. To Reduce the volume of surgical intervention, preventing recurrence and metastasis after surgery and / or radiation and radiotherapy (for Ewing tumors, breast cancer, colon cancer, etc.).**

**Chemotherapy before surgery to try to reduce the size of the tumor and the extent of the surgery is called neoadjuvant chemotherapy.**

**Chemotherapy after surgery to suppress possible tumor metastases is called adjuvant chemotherapy.**

**Chemotherapy with low doses to maintain remission is known as maintenance chemotherapy.**




| Chemotherapeutic agents | |
|---|---|
| **Cycle specificity** | **Cycle nonspecificity** |
| Act against replicating cells | Act against as replicating cells as an tumor with alow percentage of replicating cell |
| Antimetabolites<br>Bleomycin<br>Alkaloids | Alkilating agents<br>Antimetabolites<br>Platinum compounds<br>Nitrozourine |

# Mechanisms of resistance of tumor cells to chemotherapy

Prevent the penetration of the cytostatic into the cell;
Acceleration of cytostatic elimination from the cell (efflux) ×;
Intensification of intracellular inactivation of the cytostatic;
Reparation of injuries;
Disruption of the metabolism of cytostatics with the formation of active derivatives;
Activation of alternative biochemical mechanisms not affected by the action of the cytostatic.

## Advantages of combined chemotherapy

I. Provides maximum cell death in the range of tolerable toxicity;

II. Effective against a wide range of cell lines in a heterogeneous tumor population;

III. May delay or prevent the development of resistant cell lines.

# Advantages of combined chemotherapy

**Examples of standard treatment regimens:**

**MORR (embichin or mustergen, vincristine or onkovin, natulan or procarbazine, pednisolone) with lymphogranulomatosis.**

**R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, onkovin, prednisolone) with non-Hodgkin's lymphoma.**

**VAMP (vincristine, methotrexate or ametopterin, mercaptopurine, prednisolone) in acute leukemia, malignant lymphomas.**

# Side effects of anticancer agents:

**BLOOD: Anemia, thrombocytopenia, leukopenia and secondary immunodeficiency;**
**SKIN: dryness, excoriation, wounds, alopecia, brittle nails;**
**GIT: inflammation of the mucous membranes, nausea, vomiting, erosion, ulcers;**
**Inhibition of spermatogenesis;**
**Mutagenicity, teratogenicity, cancerogenicity.**

## Side effects of anticancer agents:

**Individual side effects:**

- Cardiotoxicity (doxorubicin, adriamycin);
- Pneumonitis, pulmonary fibrosis (bleomycin, nitrosourea derivatives);
- Polyneuritis (vinblastine and vincristine);
- Hepatotoxicity (methotrexate);
- Nephrotoxicity (platinum preparations), etc.

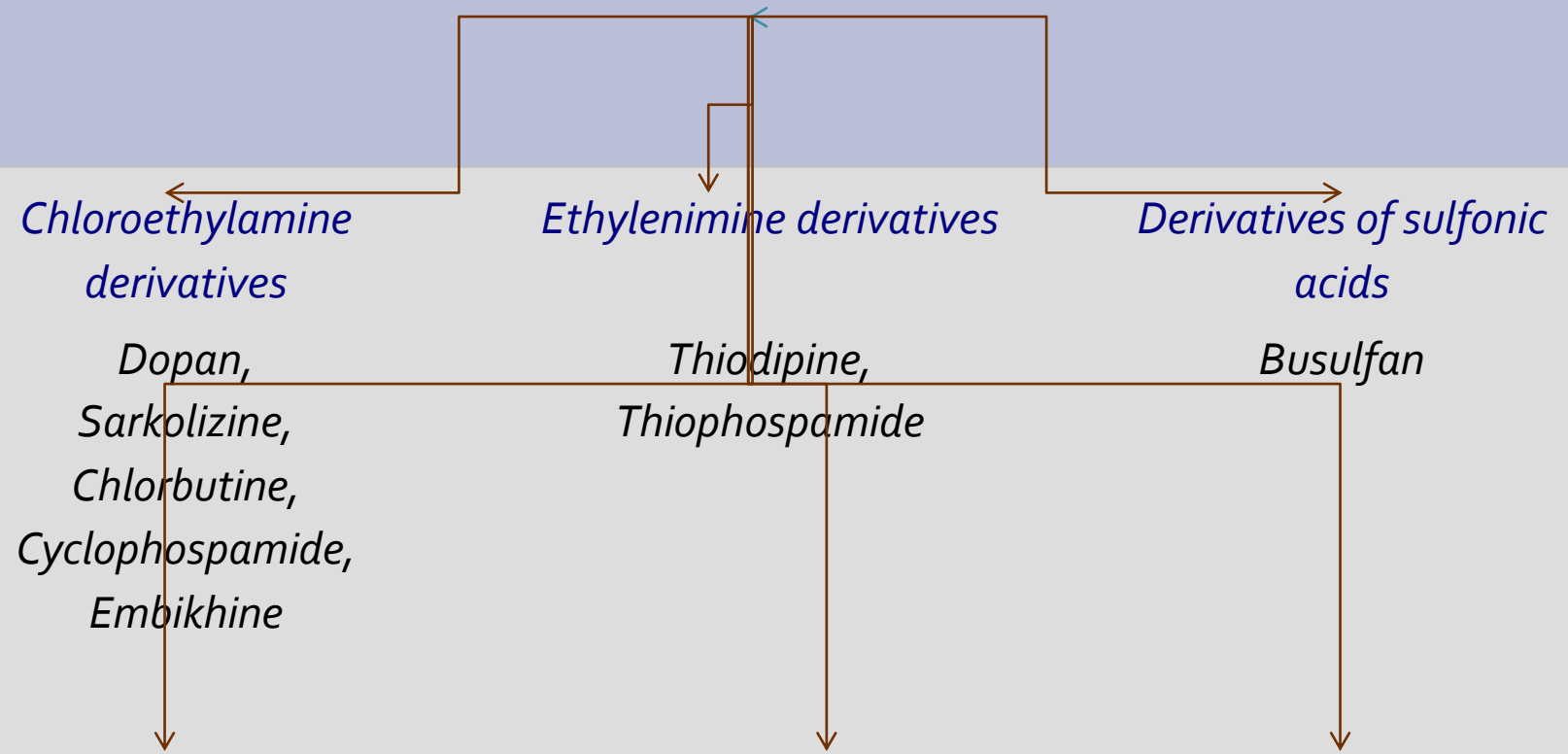
## Contraindications to chemotherapy

- Pregnancy and lactation;
- Severe cardiopulmonary insufficiency;
- Severe liver and kidney damage;
-Decompensated diabetes mellitus;
- Severe anemia (hemoglobin less than 60 g / l), leukopenia (less than 3 million in a liter), thrombocytopenia (less than 1 million in a liter);
- Allergies;

# Classification of antitumor agents

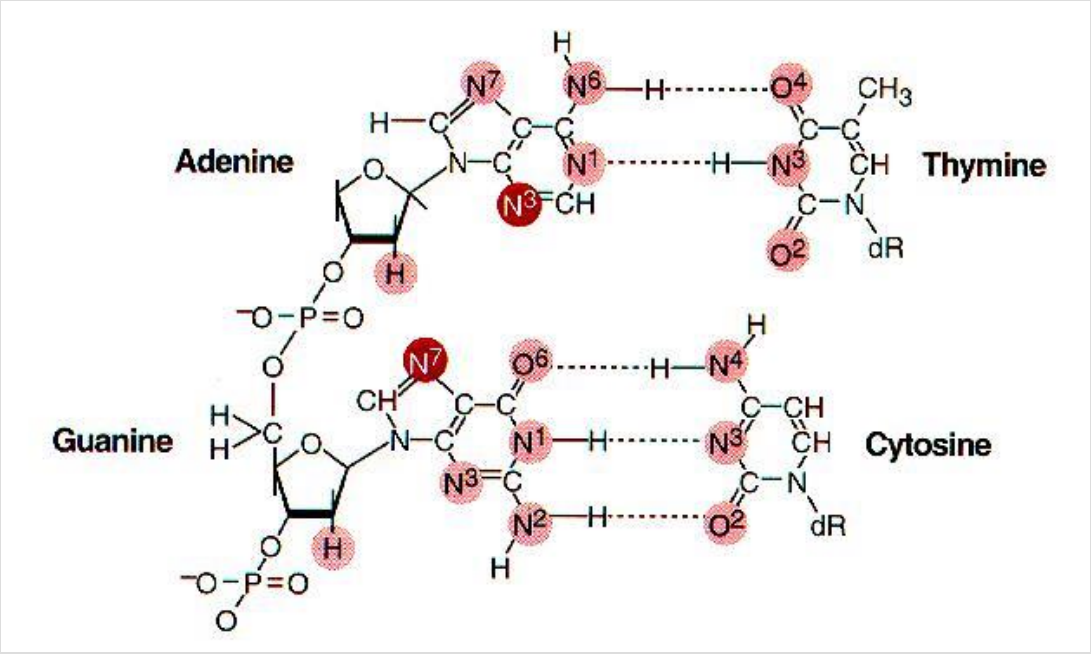
Alkylating compounds.
Antimetabolites.
Synthetic compounds of different groups.
Preparations of plant origin.
Antibiotics with anticancer activity.
Enzyme preparations.
Hormones and antagonists.
Targeting preparations: monoclonal antibodies and protein kinase inhibitors.
Cytokines.
Bisphosphonates.

# Alkylating compounds



# The mechanism of the antiproliferative effect of alkylating compounds

Contain alkylating groups that can bind to nucleic acids and proteins.
Usually, there are two alkyl groups that cause cross-linking in DNA molecules and violate replication.
Alkylation of RNA leads to a breakdown in protein synthesis.



# *Cyclophosphamide*

**Mechanism of action: associated with the formation of metabolites that have an alkylating effect.**

**Indications:**
**Lymphoproliferative diseases.**
**Neuroblastoma.**
**Ewing's tumor.**
**Lung cancer.**
**Cancer of the ovaries.**

# *Indications for some alkylating agents*

***Thiophosphamide (thiotepa, thiothef, imiphos):***

- ***Cancer of breast, ovary, lung, bladder;***
- ***Mesothelioma of the pleura;***
- ***Malignant diseases of meninges;***
- ***Lymphoproliferative diseases;***

***Busulfan:***

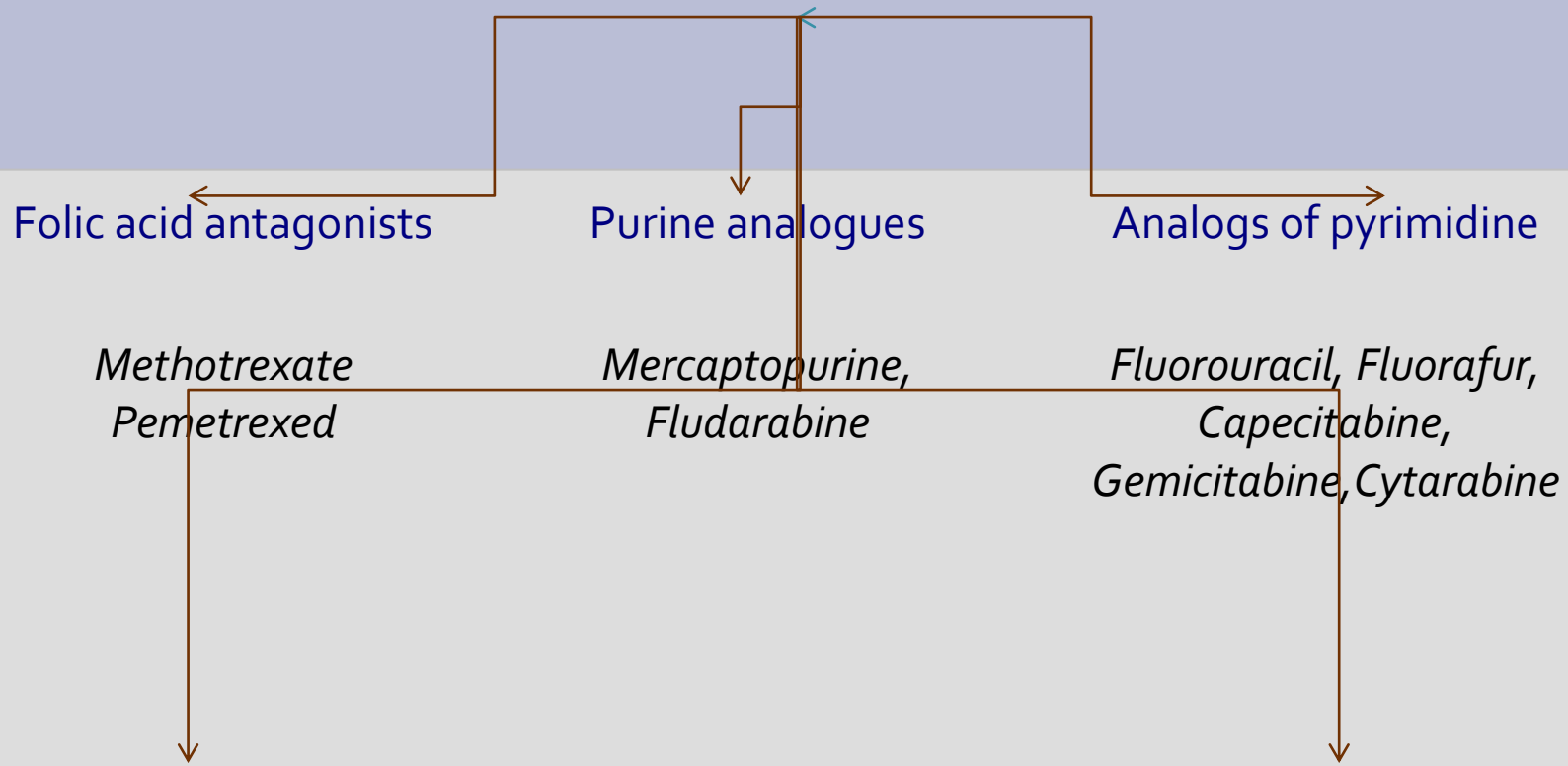
- ***Tumors of the hematopoietic organs;***
- ***preparation for bone marrow transplantation;***

# *Indications for some alkylating agents*

***Carmustine:***
***-Brain tumors - as part of combination therapy in patients with relapse of the disease;***

***Carboplatin:***
***-The nature of the organs of the reproductive system;***
***-The cancer of the lung;***
***-Malignant neoplasms of the head and neck;***
***-Soft tissue sarcoma;***
***-Melanoma;***

# Antimetabolites



# *Methotrexate*

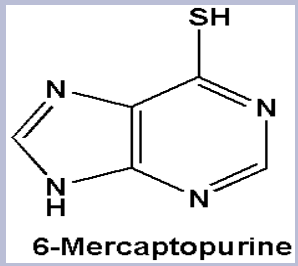
Mechanism of action: is an analog of folic acid. It blocks the dihydrofolate reductase and prevents the conversion of dihydrofolates to tetrahydrofolate (necessary for the synthesis of purines and thymidylate) → violates the synthesis of DNA, RNA and protein.

Indications:
Chorion carcinoma.
Acute lymphatic leukemia.
Breast cancer.
Tumors of the head and neck.
Cancer of the lungs, bladder, stomach.
Osteosarcoma.
Rheumatoid arthritis.
Psoriasis.

# Pemetrexed

Mechanism of action: inhibits dihydrofolate reductase, thymidylate synthase (TS) and glycinamide-ribonucleotide-formyl transferase (GARFT). In the cell it is converted into polyglutamate forms with a longer T1 / 2, which are more typical for tumor cells than for normal cells, which increases the effect in tumor cells.
Indications:
locally distributed or metastatic non-cell lung non-small cell lung cancer;
malignant pleural mesothelioma;

# Mercaptopurine



6-Mercaptopurine

Mechanism of action: Mercaptopurine → mercaptopurine-ribosophosphate → ↓ formation of purine ring and adenosine monophosphate + converted to mercaptopuguanine, included in RNA and DNA → synthesis of non-functional RNA and DNA. Also ↓ angiogenesis.

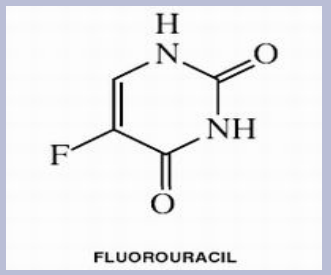
Indications:

acute lymphoblastic leukemia.

acute and chronic myelogenous leukemia.

chorionepithelioma of the uterus.

# Fluorouracil



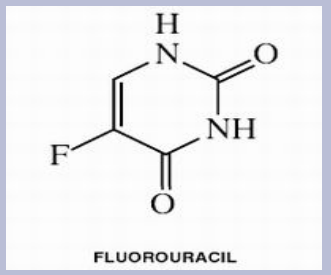

Mechanism of action: analogue of pyrimidine. Its active metabolites inhibit thymidylate synthetase and cause thymidine deficiency, and are also involved in the synthesis of RNA and disrupt protein synthesis.

Indications:

slowly growing solid tumors (colon, breast, ovaries, pancreas, stomach).

basal cell carcinoma (topically).

# Capecitabine



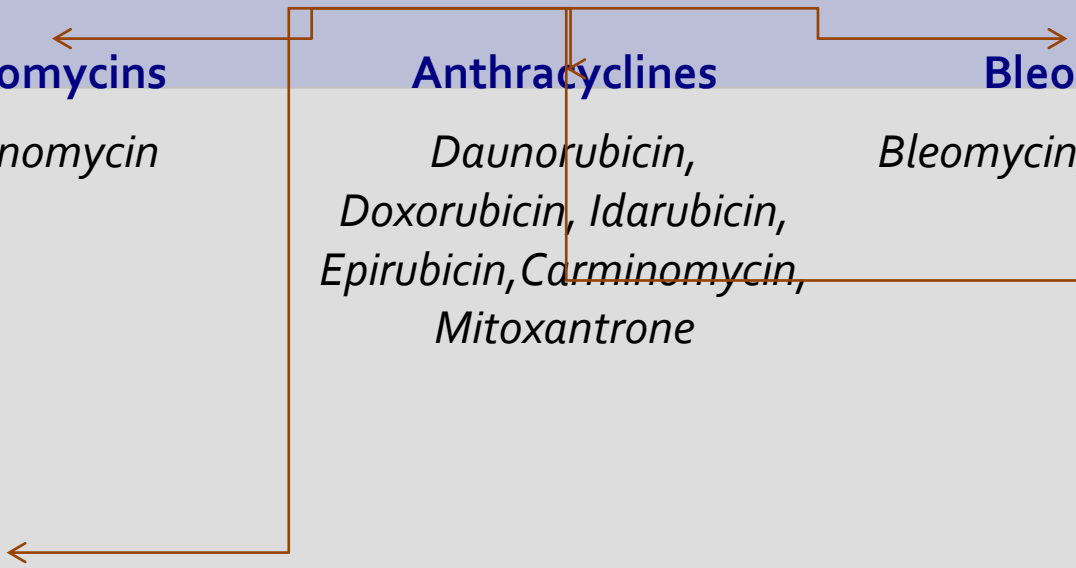

Mechanism of action: it is converted into 5-fluorouracil (5-FU) in tumor tissue (under the influence of tumor angiogenic factor thymidine phosphorylase), which minimizes the systemic effect of 5-FU on healthy tissues.

Indications:

breast cancer with metastases

colon cancer with metastases

# Anticancer antibiotics



**Actinomycins**

*Dactinomycin*

**Anthracyclines**

*Daunorubicin, Doxorubicin, Idarubicin, Epirubicin, Carminomycin, Mitoxantrone*

**Bleomycins**

*Bleomycin, Bleomicetin*

**Derivative Of aurelic acid**

*Olivomycin*

**Other**

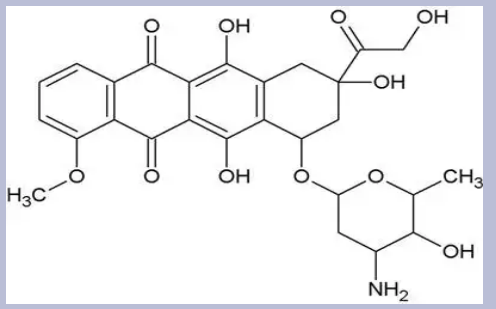
*Bruneomicin*

*Mitomycin*

# The mechanism of antiproliferative action of antibiotics

Integrate (intercalate) into DNA → ↓ transcription and replication + DNA strand breaks are formed;
Topoisomerases I and II are suppressed;
Produce free radicals → oxidize the nitrogenous bases of DNA and violate the integrity of CPM (anthracyclines, bleomycin);
Causes apoptosis of cells by activation of the protein p53 and caspases (anthracyclines)
These are cyclonespecific drugs. An exception is bleomycin.

# Anthracycline antibiotics

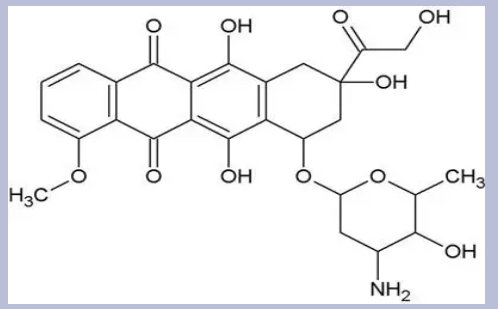



Anthracyclines and their derivatives are among the most powerful antitumor drugs.
Natural: daunorubicin, doxorubicin, carminomycin,
Synthetic: idarubicin, epirubicin, mitoxantrone.

Side effects: as in all cytostatics + necrosis when getting under the skin + cardiotoxicity (especially daunorubicin and doxorubicin) due to lipid peroxidation.

Less cardiotoxic synthetic anthracyclines.

# Anthracycline antibiotics




Indications for doxorubicin:
Sarcomas
cancer of the breast, lung, thyroid, urinary tract and genital organs
lymphoproliferative diseases

Reduction of cardiotoxicity of doxorubicin is achieved by encapsulating it in liposomes, and addition of antioxidants (tocopherol, β-carotene, coenzyme Q) to therapy.

# Anticancer agents from plants (microtubules inhibitors)

**Inhibitors of mitosis**

***Vinkalkoloids***

*Vinblastine*

*Vincristines*

***Taxanes:***

*Paclitaxel,*
*Docetaxel*

**DNA topoisomerase inhibitors**

***topoisomerases I:***

*Topotecan, Irinotecan*

***topoisomerase II:***

*Etoposide, Teniposide*

# Inhibitors of mitosis (metaphase poisons)

Vinka alkaloids pink (vinkaalkaloids): vinblastine, vincristine
Communicate with tubulin → depolymerization of microtubules →
stop cell division and their death
are rapidly absorbed by leukocytes and platelets
relatively non-toxic, but can cause neuromuscular damage.

Indications:
lymphoproliferative diseases,
tumors testicles,
chorioepithelioma,
cancer of the urinary tract,
lung cancer

# Inhibitors of mitosis (metaphase poisons)

Yew tree alkaloids (taxanes): paclitaxel, docetaxel
Communicate with tubulin → ↑ polymerization of microtubules → stop cell division and their death. They are active in the G2 / M phase of mitosis.

Indications:
cancer of the ovaries,
mammary cancer,
non-small cell lung cancer, squamous cell carcinoma of the head and neck,
cancer of the bladder,
esophageal carcinoma,
leukemia,
Kaposi sarcoma in patients with AIDS.

# Topoisomerase inhibitors of DNA

Topoisomerase I inhibitors: topotecan, irinotecan
Communicate with the topoisomerase-DNA complex → prevent respiralization (in the S-phase of the cell cycle).

Indications for topotecan:
ovarian cancer,
lung cancer,
myelodysplastic syndrome,
chronic myelomonocytic leukemia

Indications for irinotecan:
Locally spread or metastatic cancer of the colon or rectum (in combination with fluorouracil and calcium folinate).

# Topoisomerase inhibitors of DNA

Topoisomerase II inhibitors: etoposide, teniposide
↓ topoisomerase II → disrupt DNA replication → ↓ cell proliferation +
↓ nucleotide transport, cause DNA strand breaks, prevent synthesis and DNA repair (in the late S and G2 phases).

Indications for etoposide:
germinogenic tumors of testis and ovaries,
cancer of the lung, stomach, bladder, adrenal cortex,
oleukiasis, non-Hodgkin's lymphoma, lymphogranulomatosis,
Ewing's sarcoma, Kaposi
chorioepithelioma,
neuroblastoma.

# Antineoplastic enzymes

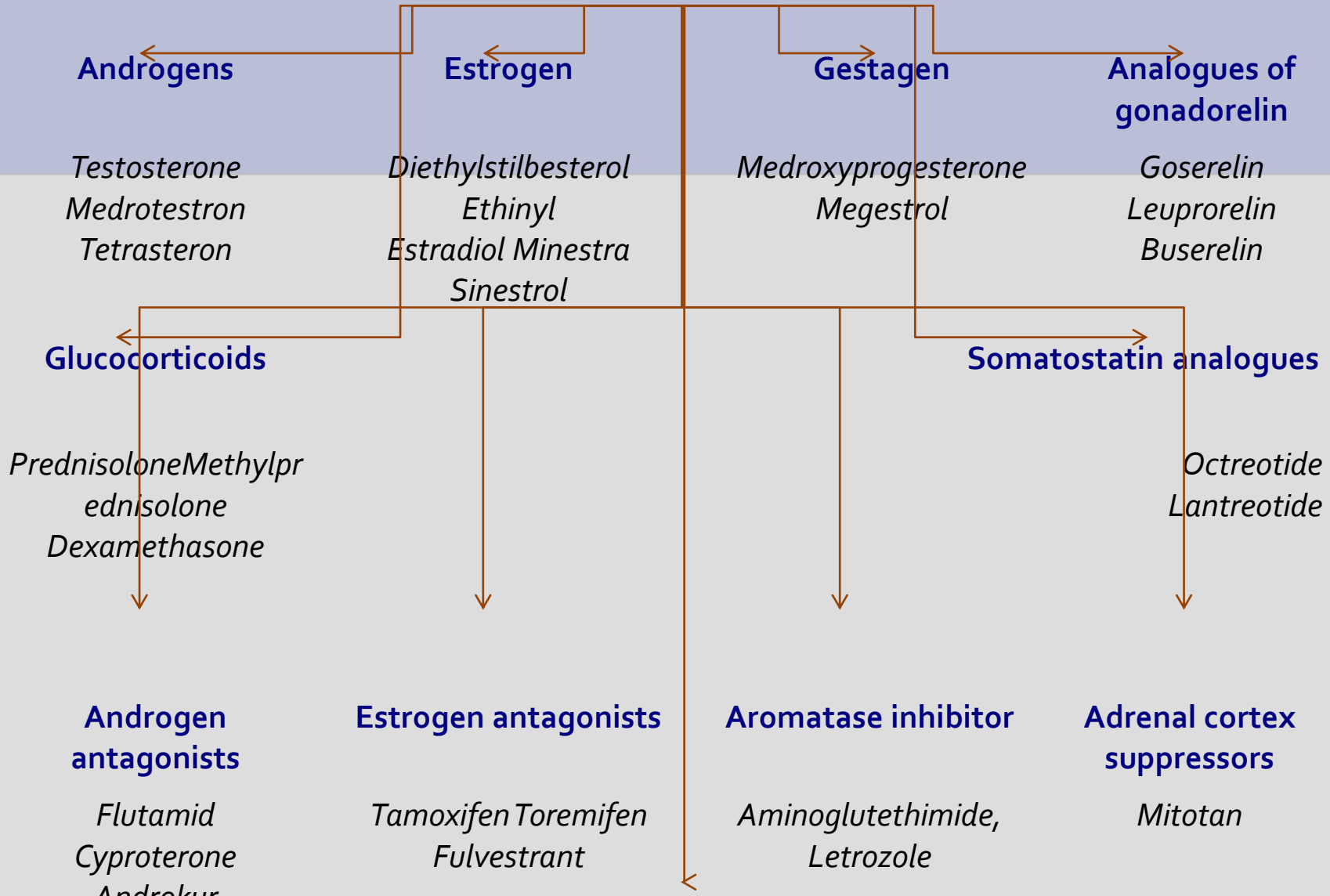
Asparaginase is an enzyme that catalyzes the cleavage of asparagine, which is necessary for the vital activity of the cell.

Asparaginase reduces the level of asparagine in leukemic tumor cells that are unable to synthesize their own asparagine → protein, DNA and RNA synthesis (in the post-mitotic G1 phase) is disrupted.

Indications:
hematopoiesis (in complex therapy)

Side effects:
bleeding,
nephro-, hepatotoxicity,
hyperglycemia,
pancreatic necrosis

# Hormones and their antagonists



# Drugs affecting the reproductive organs

Mechanism of action: humoral regulation of cell function, stimulation of differentiation and inhibition of cell division.

| | Indications |
|---|---|
| **Androgens** | Breast cancer;<br>Hysteromyoma;<br>Endometriosis |
| **Antiestrogens** | Breast cancer;<br>Endometrial cancer;<br>Estrogen-dependent tumors |
| **Gestagens** | Cancer of breast; endometrium, ovaries<br>Prostate cancer |
| **Antiandrogens** | Prostate cancer |
| **Analogues of GnRH** | Prostate and breast cancer (pharmacological castration) |

# Monoclonal antibodies (mAbs)
## I. Nonconjugated mAbs

1) Rituximab (Rituxan, MabThera) is the first mAb approved for use in oncology.
This chimeric mAb, which has a variable mouse and constant human region. Specifically binds to CD20 on B-lymphocytes → initiation of antibody-dependent cell-mediated cytotoxicity (AZPC) → lysis of B cells.

Indications:
B-cell non-Hodgkin's lymphomas,
B-cell large-cell lymphomas,
rheumatoid arthritis (some variants)

# Monoclonal antibodies (mAbs)
## I. Nonconjugated mAbs

2) Alemtuzumab (Mabcampas, Kampas) is a humanized mAb to CD52.
CD52 antigen is expressed on the membrane of most mature normal and tumor T and B lymphocytes, monocytes, thymocytes and macrophages with very high density (about 5%). It starts AZKTS and complement-dependent cytotoxicity.

Indications:
Chronic lymphatic leukemia

# Monoclonal antibodies (mAbs)
# I. Nonconjugated mAbs

3) Trastuzumab (Herceptin)

Mechanism: mAbs selectively interact with protein-receptor-2 (HER2) to EGF on malignant cells and inhibit their proliferation. Cell-mediated cytotoxicity is more pronounced with respect to tumor cells overexpressing HER2.

Indications:

breast cancer (in combination with paclitaxel)

# Monoclonal antibodies (mAbs)
# I. Nonconjugated mAbs

4) Bevacizumab (Avastin)

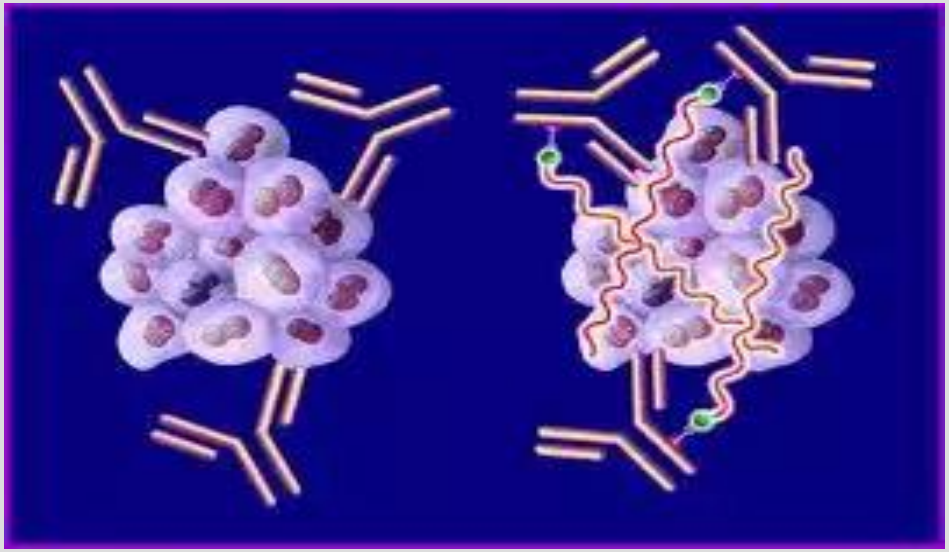
Mechanism: mAT selectively bind and neutralize endothelial growth factor of vessels (VEGF) → ↓ vascularization and suppression of tumor growth.

Indications:

Metastatic cancer: colo-rectal, renal cell, lung, breast, glioblastoma IV degree

# Monoclonal antibodies (mAbs)
# II. Conjugated mAbs

The conjugated mAbs are divided into the following groups:
with radioactive particles (radioimmunotherapy);
with cytostatics;
with toxins (or immunotoxins).
Currently, only two mAbs connected to radioactive particles are registered for tumor therapy in the world.



# mAT, combined with radioactive isotopes

Ibritumomab tiuxetan (Zevalin) - mAb to CD20, connected to 90Y, which releases β-radiation, its penetration depth is 5 mm, its effect is directed mainly on tumor cells.
Zevalin binds non-specifically to B-lymphocytes, therefore, pre-inject Rituximab to block normal B cells. → Zevalin specifically bind to lymphoma cells, which ↑ deliver the drug to the tumor and ↓ spread the radioactivity throughout the body.

Indications:
- B-cell CD20 + non-Hodgkin's lymphoma in adult patients;
- Follicular lymphoma.

# mAT, combined with radioactive isotopes

Tozitumomab (Bexar) - mAT to CD20, connected to 131I. (not registered in Russia)

Indications:

- recurrence of follicular lymphoma

The mode of application of Beksar includes two stages: dosimetric and therapeutic itself. 131I decays, releasing β- and γ-radiation with a half-life of 8 days. At the time of treatment, the isolation of the patient and the special conditions of his stay in the hospital are required, since the radioactive isotope 131I is excreted in the urine.

# Inhibitors of protein tyrosine kinases

***Imatinib (Gleevec)***
***Nonselectively inhibits:***
***mutant protein tyrosine kinase Bcr-Abl (its gene is located on the Philadelphia chromosome Ph),***
***a mutant tyrosine kinase receptor c-Kit (CD117, a receptor for growth factor of mast and stem cells)***
***tyrosine kinase receptor of platelet-derived growth factor.***

***Thus, imatinib inhibits signaling in cells and cell proliferation, causing their apoptosis.***

# Inhibitors of protein tyrosine kinases

*Imatinib (Gleevec)*
*Indications:*
*chronic myeloid and acute lymphoblastic leukemia (in mono- and combination therapy),*
*systemic mastocytosis,*
*hypereosinophilic syndrome and / or chronic eosinophilic leukemia,*
*malignant gastrointestinal stromal tumors,*
*bulging dermatofibrosarcoma.*

*Dasatinib (Spriceil) is used for resistance to imatinib.*

# Inhibitors protein tyrosine kinase

Lapatinib (Tyverb) is the first double reversible selective tyrosine kinase inhibitor ErbB2 (ErbB1) and HER2 + / neu (ErbB2 +), and the type I epidermal growth factor receptor.

Indications:

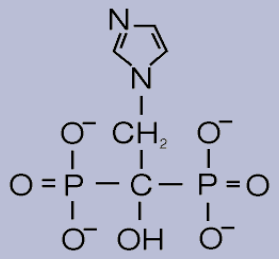
common and metastatic breast cancer.

# Inhibitors of protein tyrosine kinases

Ibrutinib (Imbruwick) is an inhibitor of Bruton tyrosine kinase, associated with the signal activity of B-cell and cytokine receptors → ↓ migration, proliferation and survival of malignant B-cells.
Indications:
The mantle cell lymphoma,
chronic lymphocytic leukemia.

To date, 24 INN inhibitors of protein tyrosine kinases have been registered in Russia

# Bisphosphonates

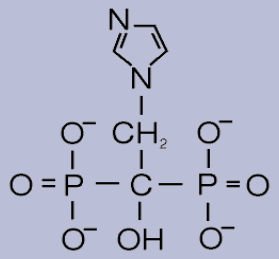


Bisphosphonates are synthetic analogs of natural pyrophosphates. They bind with calcium and accumulate in high concentration only in bones.

Oncology uses: Pamidronic acid, Clodronic acid, Zoledronic acid

Mechanism of action:
inhibit the activity of osteoclasts;
induce apoptosis of osteoclasts;
change the signaling between osteoclasts and osteoblasts;
form a chemical barrier between bone and osteoclast.

# Bisphosphonates



Indications:
Multiple myeloma;
Metastases in the bone of solid tumors (with the aim of arresting the pain syndrome and preventing secondary fractures);
Hypercalcemia due to malignant tumor