Cytostatics

Types of chemotherapeutics according to the mechanism of action ::

1. Mitosis inhibition
   - *Inhibition of microtubule polymerization :*: vinca alkaloids (vincristine, vinblastine, vinorelbine)
   - *Microtubule hyperstabilization*: taxanes (paclitaxel, docetaxel)
2. Inhibition of DNA replication
   - *DNA precursors - antimetabolites (S phase)*: antifolates, purine analogues, pyrimidine analogues, ribonucleotide reductase inhibitors
   - *Topoisomerase inhibitors (S phase)* : topoisomerase I inhibitors, topoisomerase II inhibitors, isomerase II inhibitors + intercalators
   - *Substances acting by alkylation or intercalation mechanism* (throughout the cell cycle): alkylating agents, platinum derivatives, non-classical alkylating agents, alkylation + intercalation
3. Other
   - *Enzyme inhibitors*: farnesyltransferases, cyclin-independent kinases (CDKi), proteasomes , PARP inhibitors

Mitosis inhibition

Inhibition of microtubule polymerization

Vinca alkaloids (vincristine, vinblastine, vinorelbine)


Vinca rosea

- first obtained from (*Vinca rosea*), now synthetic
- they bind tightly to cellular microtubules and block their function
- the place of binding is the microtubular protein tubulin, it specifically binds to both its subunits (α and β) during the S phase of the cell cycle
- binding to tubulin terminates the formation of microtubules , it causes their depolymerization and dissolution of the mitotic spindle
- the result is **mitosis arrest**
- they also affect microtubules, which enable chemotaxis, migration, intracellular transport, organelle movement...

Side effects:

- **vincristine**: neurotoxicity (the largest of the vinca alkaloids) - paresthesia on acres, impaired muscle reflexes, muscle tone, motor and paralytic ileus , skin reactions, hypertension or hypotension , cardiovascular disorders, optic nerve atrophy or cortical blindness, polyuria, dysuria, impaired ADH secretion , bronchospasm, alopecia (hair loss) is not common / in hematological malignancies
- **vinblastine**: neurotoxicity (less)
- **vinorelbine**: neurotoxicity (smallest), krátkodobá reverzibilní myelosuprese, minimální emetické působení, short-term reversible myelosuppression, minimal emetic effect, intravenous use may cause phlebitis / in breast cancer lung and haematological tumors

Microtubule hyperstabilization

Taxanes (paclitaxel, docetaxel)

- cytostatics made from the plant alkaloid taxol from the bark of the tree *Taxus brevifola* (Pacific yew), currently obtained semisynthetically from a plant precursor obtained from the needles of the European yew *Taxus baccate*
- it also binds to microtubules, but the binding place is different
- taxane binding inhibits microtubule depolymerization, which normally occurs in the cell at the end of cell division (during the transition from metaphase to anaphase)
- cells with undecomposed tubules cease to divide and grow
- taxanes penetrate well into body cavities, or into the retinal fluid (effusion), do not penetrate the CNS, excretion by the hepatobiliary route

Side effects::

- **common**: neutropenia , hypersensitivity reactions due to histamine release , cardiac arrhythmias, allergic reaction may progress to anaphylaxis , neurotoxicity, fluid retention, inflammation at the site of paravenous administration or during the infusion into which they were infused
- **paclitaxel**: neurotoxicity (peripheral polyneuropathy), alopecia , emetogenic, mucositis, anorexia nervosa , joint, muscle pain, necrosis during paravenous leakage / breast and ovarial cancers
- **docetaxel**: granulocytopenia, hypersensitivity reactions, emetogenic, anorexia, mucositis, artalgia, myalgia, dermatotoxicity

Inhibition of DNA replication

DNA precursors - antimetabolites (S phase)

Antifolates (folic acid analogues)

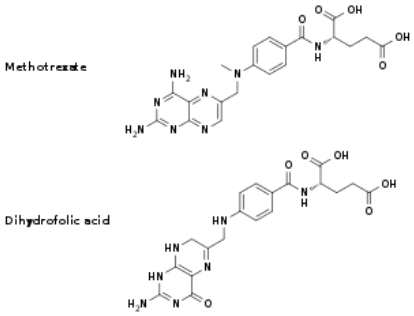
Methotrexate

- inhibits the enzyme ***dihydrofolate reductase***, which is responsible for the reduction of folic acid to tetrahydrofolic acid
- after its application, the concentration of tetrahydrofolate in the cell decreases sharply
- tetrahydrofolate, a coenzyme-transfer monocarbon radical (methyl, formyl and methylene groups) that is needed for the synthesis of purine bases and for NK repairs
- methylenetetrahydrofolate is further required for the conversion of deoxyuridine monophosphate to deoxythymidine

monophosphate
- NA synthesis is then disrupted in several stages, but these mechanisms affect both tumor and healthy cells
- however, tumor cells should be more affected because they have a more intense process of polyglutamylation (binding of glutamyl groups to methotrexate), polyglutamyl forms of methotrexate have a greater affinity for dihydrofolate reductase
- the antidote is leucovorin-tetrahydrofolic acid

Side effects::

- toxic manifestations mainly on endothelial and epithelial tissues (mucous membranes, skin), on the skin can cause photosensitivity, itching, rash, toxic skin reaction and very rarely Lyell's syndrome, alopecia, vomiting, diarrhea, toxic mucositis, intestinal bleeding, ulceration of the oral mucosa and whole gastrointestinal tract, toxic to the gonads, decrease in neutrophils and platelets, long-term administration of small doses can cause liver damage (fibrosis) osteoporosis , high doses have direct nephrotoxic activity / in osteogenic sarcoma, immunosuppressive indication is psoriasis , psoriatic and rheumatoid arthritis



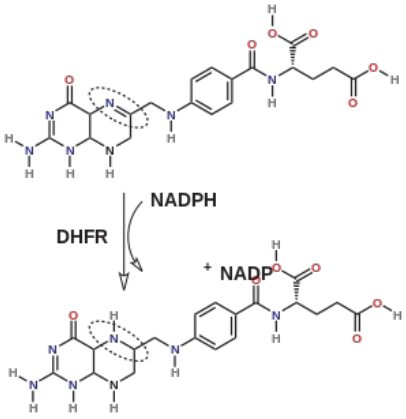
Methotrexate-dihydrofolate comparison

Pemetrexed

- is similar to folic acid - inhibits:
  1. dihydrofolate reductase
  2. thymidylate synthase (deoxyuridine + N5, N10 methyl 4HF → dTMP)
  3. glycinamide ribonucleotide formyltransferase

Leucovorin (folinic acid)

- tetrahydrofolic acid metabolite derivative (reduced forms of folic acid)
- tetrahydrofolate source - does not require DHFR activity
- it is used at high doses of methotrexate or with 5-FU (increasing the activity of some enzymes increases the effect) - cancer of GIT



Methotrexate inhibited reaction (reduction of dihydrofolate to tetrahydrofolate)

Purine analogs

They act::

1. inhibition of adenosine deaminase – **Pentostatin**
2. thiopurines inhibit purine synthesis and metabolism – **Merkaptopurine**

Side effects:

- myelosuppression, toxic mucosal damage, indigestion (stomatitis, diarrhea), reversible hepatotoxicity / in acute lymphocytic leukemia and other malignant lymphoproliferative diseases

Pyrimidine analogues

5-fluorouracil (5-FU), capecitabine, gemcitabine

- inhibit thymidylate synthase (5-FU, Capecitabine) – cancer of GIT
- inhibit DNA polymerase
- inhibit ribonucleotide reductase (Gemcitabine) – cancer of pancreas
- inhibit DNA methylation

Side effects:

- **5-FU**: mucositis, myelosuppression, alopecia, photosensitivity, hand-foot syndrome, hyperpigmentation / cancer of lungs, breast and GIT
- **capecitabine**: only rarely myelotoxicity and alopecia, nausea, vomiting, diarrhea
- **gemcitabine**: myelosuppression, influenza symptoms, less often mucositis and hepatotoxicity, emetic potential is not significant, alopecia is not common during monotherapy, nephrotoxicity with proteinuria and hematuria, dyspnoea or bronchospasm are rare

Ribonucleotide reductase inhibitors

Hydroxyurea

- a compound chemically similar to urea
- in the cell the enzyme blocks ribonucleotide reductase, which is responsible for the conversion of ribonucleotides to the corresponding deoxyribonucleotides
- block of this enzyme stops the production of deoxyribonucleotides
- however, it also inhibits pyrimidine synthesis
- hese mechanisms damage cells mainly in the S-phase

Side effects:

- myelotoxicity, rash, hyperpigmentation, digestive problems, nausea, vomiting, anorexia, elevated liver transaminases, hyperbilirubinemia, neurological problems, fatigue, micturition disorders, kidney function, fever, acute pneumonitis, pigmented nail strips

Topoisomerase (S phase) inhibitors

Topoisomerase I inhibitors

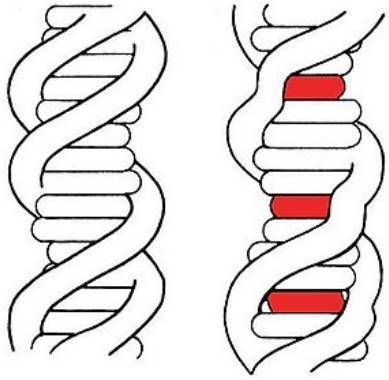
Topotecan – ovarial cancer + SCLC

Irinotecan – cancer of colon

Topoisomerase II inhibitors

Etoposide – lung and testicular cancers...

Topoisomerase II inhibitors + intercalators


intercalation

Anthracyclines (anthracycline ATB)

- produced by *Streptomyces*
- in addition to inhibiting topoisomerase II, it also acts intercalating

Doxorubicin, **Epirubicin** – breast cancer, ovarial cancer, hematological malignancies...

Substances acting by an alkylation or intercalation mechanism (throughout the cell cycle)

Alkylating agents

- they contain reactive alkyl groups (electrophilic) in their structure, these electrophilic groups attack negatively charged (nucleophilic - electron-rich) parts of molecules
- nucleophilic groups represent those places of molecules where there are oxygen, nitrogen or phosphorus atoms (these are amino groups, imidazole, carboxyl, sulfhydryl or phosphate groups)
- the electrophilic group forms a nucleophilic covalent bond
- alkylation of DNA causes many defects, detachment of the purine base, breaks in one or two strands of DNA, internal bonds in the chain or between chains, thus damaging the genetic information of the cell and if not repaired in time, the cell dies
- the effectiveness of alkylating cytostatics is thus dependent on the activity of the repair mechanisms of individual cells
- eg. **cyclophosphamide** – used in hematological malignancies, a strong immunosuppressant

Side effects:

- in general: By being able to kill even slowly proliferating tumor cells, they also damage slow-proliferating hematopoietic stem cells, causing long-term and sometimes permanent damage. Furthermore, amenorrhea, oligospermia leading to permanent infertility, mutagenic and carcinogenic effects that can cause acute leukemia or myelodysplastic syndrome
- **cyklophosphamide**: myelosuppression, urothelial toxicity, vomiting, alopecia, renal impairment, pulmonary fibrosis, ADH secretion disorder, transient DM

Platinum derivatives

Cisplatin, **karboplatin**, **oxaliplatin**

- they do not alkylate in the true sense of the word - they do not have an alkyl group - only a similar effect as alkylating agents
- it binds to DNA to form intercalation bonds that prevent replication and repair processes
- the basis of combined chemotherapeutic regimens of many solid tumors (sarcomas, ovarial cancers, lung cancers...)

Side effects:

- **cisplatin**: highly nephrotoxic, impairs tubular function, manifested by decreased glomerular filtration and isolated Mg losses, which can lead to tetany, peripheral neuropathy and hearing damage, Corti organ damage is irreversible, hearing loss for high tones is common, optic nerve damage , cortical blindness or papillary edema are exceptional, emetogenic effect
- **karboplatin**: less neurotoxic, hematopoietic depression, less ototoxicity, alopecia, less emetogenic, dermatitis, mucositis, allergic reactions, itchy skin, taste changes
- **oxaliplatin**: sensory neuropathy (dysesthesia of limbs, face and mouth), swallowing disorders , nausea, vomiting, not nephrotoxic and ototoxic

Non-classical alkylating agents

Dacarbazine – malignant melanoma, hematological malignancies
Temozolomide – glioblastoma G IV

Alkylation + intercalation

Bleomycin

- glycopeptide ATB
- product of streptomycete
- HD, testicular tumors

Mitomycin

- product of streptomycete
- breast cancer, bladder cancer,...

Other

Enzyme inhibitors

Farnesyltransferase inhibitor

Tipifarnib (FTaseI)

- prevents the attachment of Ras protein to the cell membrane
- unfortunately, by blocking farnesyltransferase, Ras (K and N) can also be modified by geranylgeranyltransferase
- blockade of both paths ↑↑↑ toxicity
- in the clinical research phase

Cyclin-independent kinase inhibitors (CDKi)

Seliciclib

- preferentially inhibits CDK2, 7 and 9
- activates malignant cell apoptosis in vitro
- in the phase of clinical trials in the indication of NSCLC and leukemia

Proteasome inhibitor

Bortezomib

- proteasome inhibitor (inhibits its chymotrypsin-like proteolytic activity)
- leads to cell cycle arrest by stabilizing negative cell cycle regulators (they are not degraded) → induction of apoptosis
- proven efficacy in mantle cell myeloma and lymphoma

PARP inhibitors

Poly ADP Ribose Polymerase inhibitor

- PARP together with the BRCA 1/2 gene product is involved in the repair of single-stranded and double-stranded DNA breaks
- more effective in tumors with a BRCA1 / 2 mutation

Olaparib

- good results in the hereditary form of breast cancer, ovarial cancer and prostate cancer

Unclassified

Trabectidin

- isolated from catfish
- indications: soft tissue sarcomas
- not fully clarified mechanism of action
- it is probably reducing molecular O2 to form superoxide by an auto-redox process near DNA → damage

Tensirolims

- specific inhibitor of mTOR (mammalian target of rapamycin) kinase, which modifies growth signaling molecules
- in case of excessive activation ↑ cyclin D and HIF - stimulation of VEGF
- cancer of kidneys, where it often has increased activity

Oblimersen

- blc2 antisense oligonucleotide - blocks the production of BCL2 protein - an inhibitor of apoptosis
- in the clinical research phase

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