Cytostatic agents

Notes of Pharmacology II practicals

This study material is exclusively for students of general medicine and stomatology in Pharmacology II course. It contains only basic notes of discussed topics, which should be completed with more details and actual information during practical courses to make a complete material for test or exam studies. Which means that without your own notes from the lesson this presentation IS NOT SUFFICIENT for proper preparation for neither tests in practicals nor the final exam.

Home preparations and revisions

You have to be able to comment these facts and terms briefly and to give examples using the knowledge from different theoretical medical disciplines.

Risk factors of cancer development:
- endogenous (gene mutations, hereditary cancer syndromes; immune system impairments)
- exogenous (lifestyle, occupational risk)

Endogenous defense (anti-cancer) mechanisms:
- on the level of a cell
- on the level of an organism

Classification of tumors according to the origin (histogenetically):
- solid tumors: carcinoma, sarcoma, neuroectodermal tumor, germinal tumor, mesothelioma, choriocarcinoma, tumor of unknown origin
- hematological malignancies – leukemia, lymphoma, myeloma

Biological characteristics of tumor:
- benign and malignant tumors

Cancer

- definition = e.g., a state, in which a particular cell population grows and proliferates quickly and with certain autonomy (out of control)

- neoplastic transformation, carcinogenesis
  - gradual process of transformation of a healthy cell in a cancer cell
  - accumulation of genetic and epigenetic changes

- What differs a cancer cell from a healthy cell?
- Which are common characteristics of cancer cells?

Treatment of a cancer disease

A) Pharmacotherapy:
- **cytostatic agents**
  - classification according to the mechanism of action
- **endocrine (hormonal) therapy**
- **targeted therapy**
  - monoclonal antibodies
  - tyrosine kinase inhibitors
  - intracellular signaling cascades inhibitors
  - others
- **immune therapy**
- **pain management, compensation of adverse effects, paliative medicine**

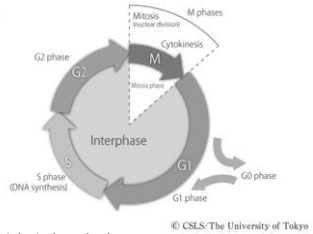
B) Surgery
C) Radiation therapy
D) Psychotherapy, rehabilitation and nutrition therapy

Cytostatics, chemotherapy

- therapeutic intention: curative, palliative
- route of administration:
  - parenterally (i.v. bolus, infusion, intrathecally, intravesically…)
  - orally
- posology: dose in mg/m^2 or mg/kg
- monotherapy and combination regimens
- repeated administration in cycles
  - pause = patient's recovery, prevention of severe AEs
    + „waking" dormant cells in G_0 phase

Cytostatics, chemotherapy

Different efficacy according to the cell cycle phase:
- *Cell cycle non-specific cytostatics* (e.g., busulfan)
- *Cell cycle specific cytostatics:*
  - Phase-nonspecific (e.g., some of alkylating agents)
  - Phase-specific (e.g., antimetabolites, taxanes)



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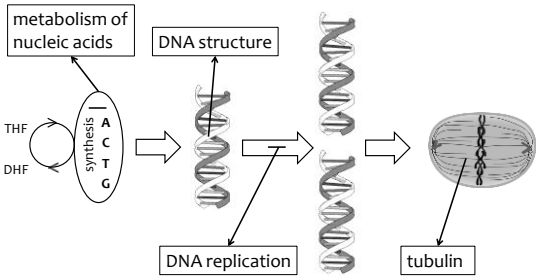
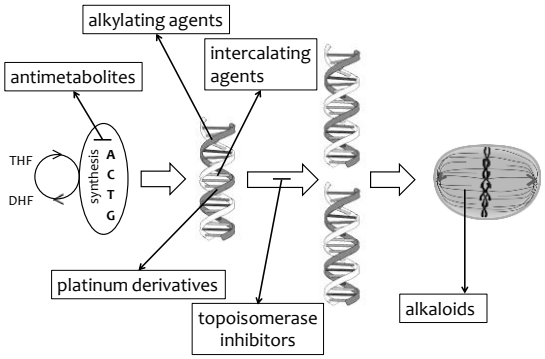
Intracelullar targets of cytostatics



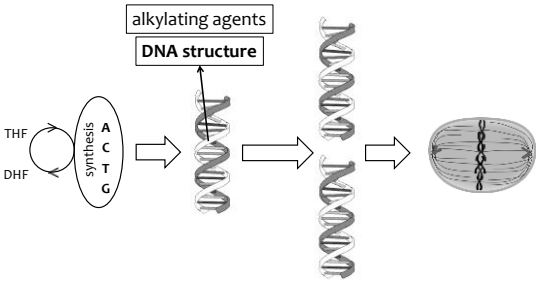
Mechanisms of action



Cytostatics according to their MoA

1. **Drugs that damage the structure of DNA**
   a) Alkylating agents
   b) Platinum derivatives
   c) Intercalating agents
   d) Bleomycin
2. **Drugs that inhibit key enzymes of DNA metabolism**
   a) Antimetabolites:
      i. Purine analogues
      ii. Pyrimidine analogues
      iii. Folic acid analogues
      iv. Hydroxyurea
   b) Topoisomerase inhibitors:
      i. Inhibitors of topoisomerase I – camptothecins
      ii. Inhibitors of topoisomerase II – podophyllotoxins
3. **Drugs that alter microtubules**
   a) Inhibitors of tubulin polymerization – *Vinca* alkaloids
   b) Inhibitors of tubulin depolymerization – taxanes
4. **Others**
   a) Drugs that inhibit protein synthesis – L-asparaginase

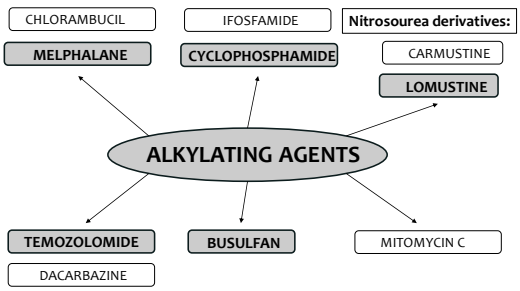
Intracelullar targets of cytostatics



Alkylating agents

- **MoA:** transfer of the alkyl group on nitrogen in nucleobases, covalent bond between two guanines of one or two DNA strands
  - Inhibition of replication, cell cycle arrest
- 50s: first derivatives of sulphur mustard in the clinical practice

- **AE – typical toxicity:** secondary malignancies – hematological



Alkylating agents

Melphalane
- i.v., p.o. administration
- treatment of hematological malignancies and solid tumors

Cyclophosphamide
- i.v., p.o. administration
- prodrugs → CYP450 → cytotoxic metabolites
- **AE:** urotoxicity, **emetogenity**
- low doses – immunosuppressant
- hematological malignancies and solid tumors

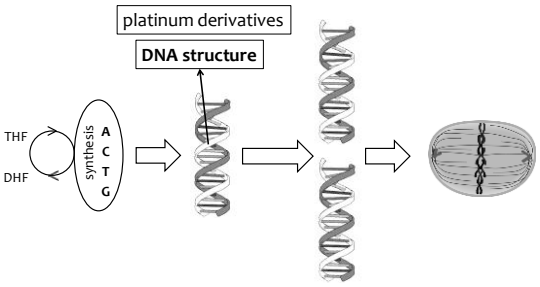
Lomustine
- p.o. administration
- lipophilic, crosses BBB → treatment of brain tumors

Alkylating agents

Temozolomide
- 100% bioavailability after oral administration
- crosses BBB → treatment of brain tumors

Busulfan
- i.v., p.o. administration
- bone marrow transplantation
- treatment of hematological malignancies

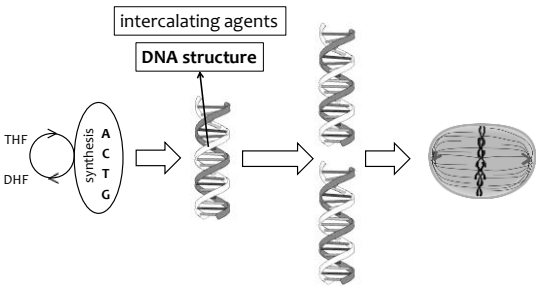
Intracelullar targets of cytostatics



Platinum derivatives

- **MoA:** binding on DNA, cross-linking of DNA strands, inhibition of topoisomerases
- **AE – most important: emetogenity, nephrotoxicity**
  - AE are dose-dependent
  - prevention of nephrotoxicity: i.v. **hydration**, forced diuresis
- **cisplatin** – high nephrotoxicity
  - treatment of solid tumors
- others:
  - carboplatin
  - oxaliplatin – typical **neurotoxicity**

Intracelullar targets of cytostatics



Intercalating agents

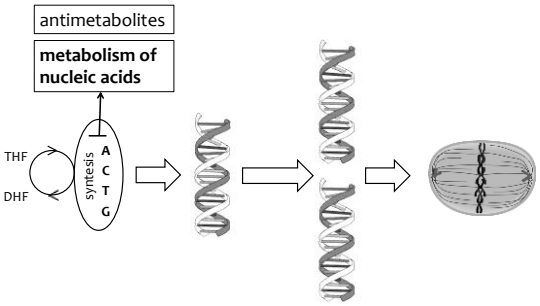
Anthracyclines

- **MoA: intercalation** = insertion between base pairs, binding of DNA strands, topoisomerase II inhibition, generation of ROS
- **AE – typical toxicity:** acute and chronic cardiotoxicity
- cardioprotective cumulative dose = restraint of therapy (e.g., doxorubicin 550 mg/m^2)
- i.v., intravesical administration
- **doxorubicin**
  - treatment of hematological malignancies and solid tumors
  - modern dosage form (PEGylated liposomes) – higher cumulative dose (860 mg/m^2)
- others: epirubicin…

Bleomycin

- mixture of glycopeptides
- **MoA:** intercalation between base pairs + inhibition of thymine incorporation → breaks → DNA fragmentation („radiomimetic" effect)
- i.v. administration
- treatment of solid tumors
- **typical AE:** fever, hyperkeratosis and hyperpigmentation of skin (flagellate = whip-like)
- risk of anaphylactic reaction

Intracelullar targets of cytostatics



Antimetabolites

- **MoA: false substrates** = affinity to target structure, loss of endogenous effect → blockade of nucleic acid synthesis, inhibition of nucleotides metabolism enzymes, production of *non-sense* DNA sequences
- prodrugs: intracellular activation mostly by phosphorylation

a) ***purine analogues*** – mercaptopurine, azathioprine, fludarabine…

b) ***pyrimidine analogues*** – fluorouracil, capecitabine, gemcitabine…

c) ***folic acid analogues*** – methotrexate, pemetrexed…

Antimetabolites – purines

Mercaptopurin

- **MoA:** inhibition of purine nucleobases biosynthesis *de novo*, inhibition of mutual conversion of purine nucleotides
- thiopurin methyltransferase (TPMT): MP → $\text{MeMP}^{\text{inactive}}$
  - **genetic polymorphism** – ↑ toxicity / ↓ efficacy
  - available pharmacogenetic testing of *TPMT*
- p.o. administration, treatment of hematologic malignancies
- azathioprine – prodrug of MP, immunosuppressant

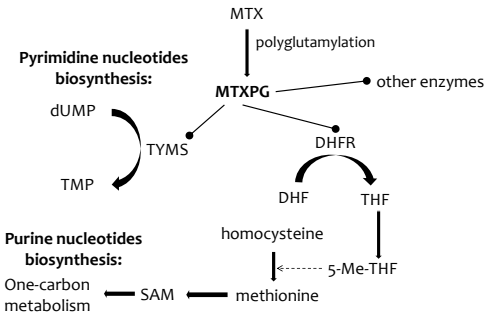
Antimetabolites – pyrimidines

Fluorouracil

- **MoA:** incorporation to RNA + inhibition of thymidylate synthetase
- combined chemotherapeutic regimens of solid cancers (i.v.)
- **AE – typical toxicity:** GIT toxicity (mucositis)
- biochemical modulation of effect: **leucovorin** (folinic acid) enhances binding on thymidylate synthetase, i.v. administered before FU
  - „FUFA" regimen = colorectal carcinoma
- capecitabine – prodrug

Antimetabolites – folic acid

Methotrexate – intracellular mechanism of action:

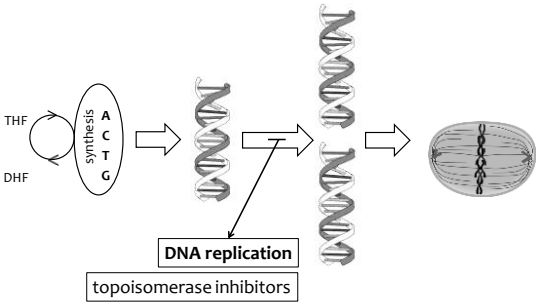


Antimetabolites – folic acid

Methotrexate

- **MoA:** inhibition of dihydrofolate reductase, thymidylate synthetase and other enzymes
- i.v., intrathecal administration, p.o.
- **leucovorin** (folinic acid) – *„rescue therapy"*, antidote
  - forces free MTX out of healthy cells ; in cancer cells, polyglutamylation is more intensive → more MTXPG → MTXPG cannot be forced out
- **TDM** – calculation of time interval from MTX administration, frequently in pediatric patients, less frequent in adults
- **AE – typical toxicity:**
  - **nephrotoxicity** – precipitation (acute renal failure)
    - prevention: hydration, urine alkalinization (pH 7–7,5)
  - pneumotoxicity
- low-dose MTX = immunosuppressant (p.o.)
- high-dose MTX = hematological malignancies and aggresive solid tumors

Intracelullar targets of cytostatics



Topoisomerase inhibitors

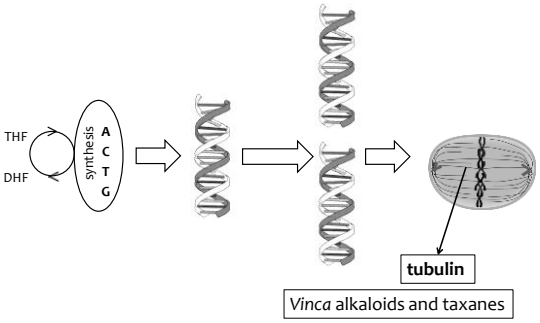
Topoisomerase I inhibitors – camptothecins

- plant-derived drugs – identification in bark of the tree *Camptotheca acuminata*
- derivatives: **irinotecan,** topotecan
  - treatment of solid tumors

Topoisomerase II inhibitors – podophyllotoxins

- plant-derived drugs – identification in *Podophyllum peltatum*
- derivatives: **etoposide,** teniposide
  - treatment of solid tumors (etoposide) and hematological malignancies (teniposid)

Intracelullar targets of cytostatics



Vinca alkaloids

- plant-derived drugs
  - identification: lesser periwinkle *(Vinca minor)*
  - isolation: *Cataranthus roseus*
- **MoA:** inhibition of tubuline dimers polymerization
  - inhibition of mitotic spindle formation, depolymerization prevails
- i.v. administration, some for p.o. (vinorelbine)
- treatment of hematological malignancies and solid tumors
- **AE – typical toxicity:** peripheral neuropathy

- original alkaloids: **vincristine**, vinblastine
- semisynthetic derivatives: vinorelbine, vindesin, vinflunine
  - increased affinity to mitotic spindle tubulin, ↓ AE

Taxanes

- plant-based drugs
  - identification and isolation: *Taxus brevifolia* (Pacific yew) a *Taxus baccata* (European yew)
- **MoA:** inhibition of tubulin depolymerization
- i.v. administration – treatment of solid tumors
- **AE – typical toxicity:** neurotoxicity
- **paclitaxel**, docetaxel, cabazitaxel

- modern dosage form: paclitaxel conjugated with albumine nanoparticles
  - transporter protein for albumine in cancer cells = better distribution from circulation into the tissues
  - ↓ toxicity, ↑ efficacy

Combination of cytostatics

- combination regimens – examples:

FUFA	fluorouracil, folinic acid
FOLFOX	folinic acid, fluorouracil, oxaliplatin
ABVD	doxorubicin, bleomycin, vinblastine, dacarbazine
BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristin, procarbazine, prednisone

Early adverse effects (AE)

- nausea, vomiting (peripheral or central mechanism)
  - **high:** cisplatin
  - **moderate:** doxorubicin
  - **mild:** fluorouracil
  - **minimal:** vincristine
- **non-specific effects:** sweating, fever, fatigue, skin corrosion, caustic effect (extravasal administration, staining)
- **specific effects:** allergy, acute cardiotoxicity

Late AE of cytostatics

- nausea, vomiting
- organ toxicity:
  - myelotoxicity (bone marrow)
  - GIT toxicity – mucositis
  - infertility, reproduction impairment (gametes)
  - alopecia (hair follicles)
  - vasal toxicity (veins)
  - hepatotoxicity
  - neurotoxicity, ototoxicity
  - nephrotoxicity, urotoxicity
  - pneumotoxicity
  - cardiotoxicity
  - secondary malignancies

Myelotoxicity

- neutropenia > thrombocytopenia > anaemia

Neutropenia

- maximum after 10–20 days, or delayed (after 4–6 weeks)
- immune suppresion – preventive measures to avoid infection
- **febrile neutropenia** – ATB treatment
- **leukocyte growth factor** G-CSF (**filgrastim**, pegfilgrastim, lipegfilgrastim), s.c. administration

Anaemia

- **erythropoietin** – epoetin α, β, ϑ, darbepoetin α (s.c.)
- vitamin B_6, B_{12}, Fe – in deficiency (p.o.)

Transfusion

- transfusion of erythrocytes, thrombocytes
- severe cases, symptomatic patients

GIT toxicity

- Nausea, vomiting, diarrhea (constipation), mucositis, or ulcerations of proximal or distal part of GIT mucosa
- Damage to teeth and gingiva, painful swallowing, heartburn (pyrosis)
- Malabsorption of nutrients, vitamins, cachexia, anorexia

→ nutritional support

Drugs used to manage GIT toxicity:

- Oral mucositis – **antiseptics** (e.g., chlorhexidine, benzydamine)
- Oral candidosis – **azole antimycotics** locally (e.g., itraconazole)
- Heartburn – **proton pumps inhibitors** (e.g., omeprazole), **antacids** (e.g., hydrotalcite)
- constipation – laxatives (**lactulose**)
- diarrhea – **antimotility agents** (loperamide), **somatostatine analogues** (octreotide)

Nausea and vomiting

Drugs used in the management of nausea and vomiting

- combined therapy, mostly preventive (p.o., i.v., p.r., etc.)
- **setrons = 5-HT_3 receptor antagonists**
  - ondansetron, palonosetron
- **NK_1 receptor antagonists**
  - aprepitant, netupitant
- **D_2 receptor antagonists and drugs with combined MoA**
  - thiethylperazine, haloperidole; olanzapine;
  - metoclopramide, itopride
- combination with corticoids (dexamethasone), antihistamines (promethazine)

- hemp *(Cannabis)* for medical use, hemp extracts

Nephrotoxicity and urotoxicity

- damage of glomerulus, interstitium, renal veins
- symptoms: asymptomatic increase of creatinine → acute renal failure
- platinum derivatives – ischemic necrosis
- methotrexate – precipitation, crystalluria

- urotoxicity: cyclophosphamide – hemorrhagic cystitis

Management of toxicity and prevention:

- hydration regimens (p.o.)
- forced diuresis (i.v. infusions of fluids, diuretics)
- urotoxicity: **mesna** (i.v.)

Neurotoxicity

- **spectrum of symptoms:**
  - **peripheral neuropathy** – paresthesia, movement coordination impairment, changes of muscle tone, fine motor skills impairment…)
  - **autonomic neuropathy** – constipation, paralytic ileus
  - **central neuropathy** – encephalopathy (headache, impairment of consiousness), meningitis, myelopathy (limb paresis), cognitive impairment, deterioration…
- Consequences may be **irreversibile**!

Management of toxicity:

- dose reduction, change of cytostatic medication
- neuropathic pain: **antiepileptic drugs** (gabapentin, pregabalin), **antidepressants** (duloxetine)
- other symptoms: Mg^{2+}, vitamin B_6, nootropics, antipsychotics…

Cardiotoxicity

- anthracyclines, bleomycin, vincristine, alkylating agents, FU…

- acute: arrhythmia, angina (chest pain)
- chronic: LV dysfunction, heart failure, congestive heart failure

- mechanism: oxidative stress, activation of intrinsic pro-apoptotic pathway

Management of toxicity and prevention:

- observation of cumulative dose
- liposomal dosage form

Other types of toxicity

Reproductive toxicity

- damage on spermatogenesis
- chromosomal aberrations, hormonal impairments
- oocytes cryopreservation before the start of the treatment
- avoid conception min. 2 month after the end of the tretment

Pneumotoxicity

- acute pneumonitis, pulmonary edema, pulmonary fibrosis
- methotrexate, bleomycin, busulfan
- cumulative doses

Other types of toxicity

Skin and skin-adnexa toxicity, blood vessel toxicity

- necrosis and corrosion (caustic effect) after extravasation
- phlebitis, thrombophlebitis, blood vessel necrosis
- hyperpigmentation and hyperkeratosis of skin
- alopecia, thinning of hair – vasoconstriction in hair follicle
  - hair (scalp) >> hair (elsewhere), eyebrows, eyelashes
  - new hair may change color and quality

Secondary malignancies

- cytostatics have mutagenic effect
- hematological malignancies
- after 10 years
- more frequent regular check-ups after the end of the cytostatic treatment

Drugs used for cancer pain treatment

- **analgetics-antipyretics, NSAIDs, opioids**
- **co-analgetics**
- bone metastases = pain, fractures → **bisphosphonates:**
  - **MoA:** inactivation and apoptosis of osteoclasts, ↓ hypercalcemia
  - affinity to metabolized bone hydroxylapatite
  - p.o. low bioavailability, i.v. infusions (oncology)
  - **AE:** p.o. – GIT irritation; i.v. – osteonecrosis of the jaw
  - **PhK:** not metabolized, excreted by urine
  - **zoledronate**
  - others: ibadronate, clodronate, alendronate, riserdronate, pamidronate
- targeted therapy – **denosumab** (**MoA:** antibody against RANKL)