Cytostatics

Notes for Pharmacology II Practicals

This study material is exclusively for students of general medicine and dentistry 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.

Thus, without your own notes from the lesson this presentation IS NOT SUFFICIENT. This presentation alone can not serve as the only study material for preparation for tests in practicals, nor for the final exam.

Cytostatics – Definition, Terminology

- drugs with cytotoxic effect used in the treatment of cancer diseases

- chemotherapeutics = synonym (english literature) → „chemotherapy“

- chemoprotectives = substances decreasing the effect of a cytostatic on healthy somatic cells

Pathophysiology of Cancer

- multifactorial disease

- endogenous risk factors:
  - Classification according to the primary tumor origin:
    - carcinoma, sarcoma, leukemia and lymphoma, neuroectodermal tumor, germinal tumor...

- exogenous risk factors:
  - Classification according to the tumor invasivity:
    - benign tumors:
    - malignant tumors:
Tumor Cell Characteristics

- hyperproliferation
- Invasivity
- ability to migrate, to create metastasis
- cell differentiation impairments → loss of replication limit
- genome instability

Treatments in Oncology

- pharmacotherapy
  - cytostatics
  - hormone therapy
  - targeted therapy
    - monoclonal antibodies
    - tyrosine kinase inhibitors
    - inhibitors of down-stream signalling pathways
  - immunotherapy
  - psychotherapy (incl., psychiatric medication)
  - nutritional therapy and treatment of adverse effects
- surgical oncology
- radiotherapy

Specifics of Chemotherapy

- parenteral or oral administration of cytostatics
- combined regimens
- dosage frequently in mg/m²

- cell cycle specificity:
  - cell cycle non-specific cytostatics
  - cell cycle specific cytostatics:
    - cell cycle phase non-specific
    - cell cycle phase specific
  - curative or palliative chemotherapy
Treatment of Cancer Pain

- NSAIDs, in case of severe pain – opioids
- combination with

- bone metastasis → bisphosphonates:
  - cause osteoclasts apoptosis
  - antiangiogenic, analgesic effect
  - i.v. infusions
  - AE: osteonecrosis of the jaw (ONJ)

  - kinematics: non-metabolized, excreted by kidneys
  - zoledronate, ibandronate, clodronate, pamidronate

Adverse Effects of Cytostatics

- early = non-specific
  - nausea, emesis (vomiting), sweating, fever, fatigue, allergy

- late = specific
  - nausea, emesis, specific organ toxicity
    - myelotoxicity (bone marrow)
    - lesions of GIT mucosa
    - infertility, reproduction impairments (gametes)
    - alopecia (hair follicles)
  - disorders of CNS and PNS
  - organ toxicity (lung, kidney, heart...)

Myelotoxicity of Cytostatics

- neutropenia, lymphocytopenia, thrombocytopenia, anemia

- febrile neutropenia

pharmacotherapy:

- hematopoietic growth factors
  - G-CSF (filgrastim)
  - GM-CSF (molgramostim)

- EPO – epoetin α, β, darbepoetin α
GIT Toxicity of Cytostatics

- nausea, emesis, diarrhea (obstipation), ulcers
- damage of teeth or gingiva, painful swallowing, heartburn
- malabsorption of nutrients, cachexia, anorexia

Pharmacotherapy:
- oral lesions – antiseptics topically (e.g. chlorhexidine)
- oral mycosis –azole antimycotics topically (e.g. itraconazole)
- pyrosis (heartburn) – PPI (e.g. omeprazole), antacids (e.g. hydrotalcite)
- laxatives – lactulose
- antidiarrheals – antimitics (e.g. loperamide)

Emesis after Cytostatics

- peripherally, or centrally induced
- high risk:
- moderate risk:
- low risk:
  - setrons = antagonists of 5-HT\textsubscript{3} receptors
    - ondansetron, granisetron, tropisetron, palonosetron
  - NK receptors antagonists – aprepitant
  - D\textsubscript{2} receptors antagonists
    - thiethylperazine, haloperidol; metoclopramide
  - glucocorticoids (dexamethasone), antihistamines

Nephrotoxicity and Urotoxicity of Cytostatics

- urotoxicity: hemorrhagic cystitis (cyclophosphamide)
- damage of glomeruli, interstitium, kidney vessels

Prevention and treatment:
- hydration regimens (p.o.)
- forced diuresis (i.v. infusions of fluids, diuretics)
- urotoxicity: mesna
Neurotoxicity of Cytostatics

- peripheral neuropathy – paresthesia, impairment of motor activity (hands)
- autonomic neuropathy – obstipation, paralytic ileus
- central neuropathy – encephalopathy (headache, disorders of consciousness), meningitis, myelopathy (extremity paresis), cognitive deficit, deterioration

Treatment:
- Dose reduction, change of cytostatic drug
- Mg²⁺, vitamin B₆, anticonvulsants, antidepressants, nootropics, antipsychotics…

Cardiotoxicity of Cytostatics

- anthracyclines, bleomycine, vincristine, alkylating agents, 5-FU…
- acute: arrhythmia, chest pain
- chronic: dysfunction of left ventricle, heart failure

prevention and treatment:
- cumulative dose
- liposomal drug forms
- dexrazoxane i.v. – chelation of Fe (?)
- treatment of heart failure: ACE inhibitors, β-blockers, digoxin, Ca channel blockers, diuretics…

Other Toxicity of Cytostatics

- reproduction toxicity
  – spermatogenesis impairment
  – chromozomal aberrations, hormonal imbalance

- pneumotoxicity
  – acute pneumonitis, lung edema, lung fibrosis
  – methotrexat, bleomycine, busulfan
  – prevention: cumulative dose
Other Toxicity of Cytostatics

- Skin, skin adnexa, and vessels
  - necrosis after unintentional extravasal administration of cytostatics
  - tromboflebitis, necrosis of vessels
  - alopecia (hair loss)

- secondary malignancies
  - mutagenic effect of cytostatics
  - hematological malignancies (leukemias)
  - up to 10 years after chemotherapy

Classification of Cytostatics

- drugs damaging the structure of DNA
  - alkylating cytostatics (alkylating agents)
  - platin derivatives
  - intercalating cytostatics
  - “radiomimetics” – bleomycin

- drugs inhibiting key enzymes of DNA metabolism
  - antimetabolites:
    - purine analogues
    - pyrimidine analogues
    - folic acid analogues
    - hydroxycarbamide (hydroxyurea)
  - topoisomerase inhibitors:
    - inhibitors of type I topoisomerase – camptothecins
    - inhibitors of type II topoisomerase – podophyllotoxins

- drugs altering microtubules
  - tubulin polymerization inhibitors – Vinca alkaloids
  - tubulin depolymerization inhibitors – taxanes

- other cytostatics
  - vitamin A derivatives – tretinoin (all-trans-retinoic acid)
  - proteosynthesis alteration – L-asparaginase

Cytostatics

Summary of drug groups

1. Drugs damaging the structure of DNA
Alkylating Agents

- alkylate guanines in the DNA, which causes covalent bonding of DNA chains
- 50’s: 1st derivatives of „nitrogen mustard” in clinics
- cell cycle phase non-specific effect, the most sensible phases are G₁ and S phase
- some drugs are cell cycle non-specific
- AE: myelotoxicity, GIT toxicity, secondary malignancies – leukemia, myelodysplastic syndrome

Alkylating Agents

a) bis(chlorethyl)amines
- mechloethamine (chloroethine), estramustine, chlorambucil, melphalan

b) oxazaphosphorines – cyclophosphamide, ifosfamide
- prodrug
- AE: urotoxicity, cardiotoxicity, pneumotoxicity, emetogenic
- hematological and solid malignancies

c) nitrosourea derivates
- cross BBB → brain tumors therapy
- carmustine, lomustine, fotemustine
- AE: late-onset myelosupression (after 6–8 weeks)

d) triazenes
- procarbazine – glioblastomas
- dacarbazine
- temozolomide

e) alkyl sulphonates
- busulfan

f) aziridines
- mitomycin C, thiotepa
Platin Derivatives
• binding on DNA, inhibition of topoisomerases
• AE: emetogenic, nephrotoxicity, ototoxicity
• TDM
• nephrotoxicity prevention:
  - hydration regimens
  - amifostine
• cisplatin
• carboplatin
• oxaliplatin

Intercalating Cytostatics
anthracyclines (cytotoxic antibiotics)
• intercalation = insertion between base pairs, non-covalent bonding of DNA chains, inhibition of type II topoisomerase, production of ROS
• AE: cardiotoxicity
• cumulative toxicity, cumulative dose
doxorubicin
  • hematological malignancies and solid tumors
  • modern drug dosage form (liposomes)
epirubicin, idarubicin, daunorubicin
doxorubicin
mitoxantrone

„Radiomimetics“ – bleomycin
• mixture of glycopeptides (cytotoxic antibiotic)
• intercalation between base pairs + inhibition of thymine incorporation into DNA → fragmentation of DNA
• solid tumors
• AE: anaphylactic reaction, skin reaction, pneumotoxicity
Cytostatics
Summary of drug groups

2. Drugs inhibiting key enzymes of DNA metabolism

Antimetabolites

- false substrates
- prodrugs

a) purine analogues – 6-mercaptopurine, 6-thioguanine, azathioprine, cladribine, fludarabine…

b) pyrimidine analogues – 5-fluorouracil, tegafur, capcitabine, gemcitabine, cytarabine…

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

Antimetabolites – Purine Analogues

6-mercaptopurine (6-MP)
- inhibition of purine bases de novo synthesis, inhibition of purine nucleotides mutual conversion

- thiopurine S-methyltransferase (TPMT)
  – polymorphism
  – pharmacogenetic screening

- hematological malignancies

- AE: myelosupression, hepatotoxicity

- azathioprine = prodrug of 6-MP – immunosupressant
Antimetabolites – Pyrimidine Analogues

5-fluorouracil (5-FU)
• incorporation into RNA + inhibition of thymidylate synthase
• solid tumors
• AE: mucositis, myelosupression, acute cardiotoxicity
• biochemical modulation of effect: leucovorin
• capecitabine, tegafur = prodrugs of 5-FU

Antimetabolites – Folic Acid Analogues

methotrexate
• inhibition of dihydrofolate reductase, thymidylate synthase and other enzymes
• TDM
• antidote leucovorine (folinic acid) – „rescue therapy”
• AE:
  – nephrotoxicity → hydration, alkalization of urine (pH 7 – 7,5)
  – pneumotoxicity, hepatotoxicity
• low dosage = immunosuppressant
• high dosage = solid and hematological malignancies

Topoisomerase Inhibitors

Inhibitors of type I topoisomerase – camptothecins
• cell cycle phase specific effect – S-phase
• irinotecan, topotecan

Inhibitors of type II topoisomerase – podophyllotoxins
• cell cycle phase specific effect – S and G2 phase
• etoposide, teniposide
• solid and hematological malignancies
Cytostatics

Summary of drug groups

3. Drugs altering microtubules

**Vinca alkaloids**

- inhibition of tubulin dimers polymerization
- **cell cycle phase specific effect** – M-phase
- hematological and solid malignancies
- **AE:** typical peripheral neuropathy

- vincristine, vinblastine
- semisynthetic derivatives: vinorelbine, vindesine, vinflunine

**Taxanes**

- inhibition of tubulin depolymerization
- solid tumors
- **AE:** neurotoxicity, hepatotoxicity

- paclitaxel, docetaxel

- paclitaxel conjugated with albumine nanoparticles
  - ↓ toxicity, ↑ effect, better distribution from circulation into tissues
Cytostatics

Summary of drug groups

4. Other cytostatics

Other Cytostatics

tretinoin (all-trans-retinoic acid)
• induces cell differentiation → inhibition of proliferation
• acute promyelocytic leukemia

asparaginase
• alteration of proteosynthesis in leukemia cells
• catalyzes decomposition of asparagine into asparagic acid and ammonia (NH₃)
• AE: hypersensitivity, anaphylactic reaction, hepatotoxicity, diarrhea

Recommended literature

• Rang & Dale’s Pharmacology, 8th ed (Humphrey P. Rang et al.), 2015

available on-line

Students should come prepared for practical lessons. Please, read the relevant chapter in the recommended textbook.