

# Anticancer therapy

## Biochemical principles of anticancer treatment

## Anticancer treatment modalities

### Local treatment:

- surgery
- radiotherapy

### Systemic treatment:

- chemotherapy
- immunotherapy
- hormonal therapy
- biological therapy

### Criteria for choosing the modality and type of medicament:

1. guidelines (international – NCCN, national – blue book, constitutional etc.)
2. specific situation (patient status and age, comorbidities, mobility, profession etc.)
3. economic aspects (centralisation of care for patients treated with expensive drugs etc.)

## Chemotherapy

- developed after World War 1, when nitrogen mustard (alkylating agent) was used for the first time.
- by interfering with the cell cycle, the neoplastic cells are prevented from another division
- the most sensitive are the rapidly multiplying cells and cells which have a decreased capacity in their reparative mechanisms.
- non-specific effect, which lead to the characteristic **side effect** of the treatment (affecting the physiologically rapidly dividing cells):
  - temporary suppression hematopoiesis (hematopoietic cells of the bone marrow)
  - GIT symptoms (gastrointestinal mucosa)
  - alopecia (cells of the hair follicles) and more

## Division according to the mode of action

 For more information see *Cytostatics*.

### Mitosis inhibitors

#### Vinca-alcaloids („mitotic poisons“) - Vinblastine, Vincristine, Vinorelbine

- Vinca-alcaloids used today are made synthetically
- they bind on the  $\beta$ -subunit tubulin and thus disrupt the dynamic growth and degradation of microtubules – microtubules don't polymerise (they depolymerise in increased concentration)
- indications: breast cancer, lung and more

#### Taxanes – Docetaxel, Paclitaxel

- diterpenes (chemically)
- originally come from a tree (pacific yew) (paclitaxel), nowadays they are produced synthetically
- bind on the  $\beta$ -subunit of polymerised tubulin increasing the affinity of the tubulin units to each other – stabilisation of microtubules of the mitotic spindle – stopping mitosis during the transition from metaphase to anaphase
- indications: breast cancer, ovary, prostate etc.

## Substances interfering with DNA replication

### DNA precursors

- **Antifolates** – prevent the normal function of folic acid in the body
  - Methotrexate – competitively and irreversibly inhibits DHFR (dihydrofolate reductase) – binds 1000 times more easily, part of many therapeutic regimens
  - Pemetrexed – structurally similar to folic acid, besides DHFR thymidylate synthase and glycylamide

ribonucleotide formyltransferase are also inhibited

- **Purine analogues**

- Pentostatin inhibits adenosine-deaminase
- thiopurines inhibit the synthesis and metabolism of purines (Mercaptopurine)

- **Pyrimidine analogues**

- inhibit thymidylát syntázu (5-FU, Capecitabine) – cancers of GIT, breast etc.
- inhibit DNA-polymerase]
- inhibit ribonucleotide-reductase (Gemcitabine) – pancreatic cancer
- inhibit DNA methylation

- **Ribonucleotide-reductase inhibitors**

- Hydroxyurea – used in Myeloproliferative diseases

## Topoisomerase inhibitors

- **Topoisomerase I inhibitors**

- topotecan – ovarian cancer + SCLC
- irinotecan – colon cancer

- **Topoisomerase II inhibitors**

- etoposide – lung cancer, testicular cancer and more

- **Topoisomerase II inhibitors with intercalating activity**

- **anthracyclines** = anthracycline ATB
- produced by strains of *Streptomyces* bacteria
- in addition to inhibiting topoisomerase II, it also acts by intercalating(they are inserted between two strands of DNA)
- Doxorubicin, Epirubicin – breast, ovarian, hematological cancers

## Substances acting by an alkylation or intercalation mechanism

- **Drugs acting by an alkylation mechanism**

- alkylating agents: transfer an alkyl group ( $C_nH_{2n+1}$ ) to the N7 of the guanine imidazole ring
- cyclophosphamide – hematological malignancies

- **Platinum cytostatics**

- they do not alkylate in the true sense of the word - they do not possess an alkyl group - only a similar effect as alkylating agents
- they bind on the DNA and form intercalating bonds that prevent replication and reparative processes
- CDDP (cisplatin), oxaliplatin, CBDCA (carboplatin) – basis of combined chemotherapeutic regimens of many solid tumors (sarcomas, ovarian cancer, lung cancer)

- **Non-classical alkylating agents**

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

- **Alkylating and intercalating agents**

- Bleomycin – glycopeptide ATBs produced by *streptomyces*
- indication: HD, testicular cancer
- Mitomycin – a product of *streptomyces*
  - breast cancer, urinary bladder cancer

## Enzyme inhibitors

### Farnesyltransferase inhibitors – Tipifarnib

- prevents the attachment of Ras protein on the cell membrane
- when inhibiting farnesyltransferase, Ras protein (K and N) can also be modified by geranylgeranyltransferase
- blockage of both pathways leads to strong toxicity of the preparation preventing its use
- in clinical research phase

### Cyclin-dependent Kinase inhibitors (CDKi) – Seliciclib

- preferentially inhibit CDK2, 7 and 9
- *in vitro* activation of apoptosis in malignant cells

- in the phase of clinical trials for the indication in NSCLC and in leukemia

### Proteasome inhibitors- Bortezomib

- proteasome inhibitor (inhibits its chymotrypsin-like proteolytic activity)
- leads to cell cycle arrest by stabilising negative cell cycle regulators (pro-apoptotic proteins aren't degraded, which leads to apoptotic induction)
- demonstrated activity in multiple myeloma and mantle cell lymphoma

### PARP inhibitors (Poly ADP Ribose Polymerase inhibitors)

- PARP together with BRCA 1/2 gene product is involved in the repair of breaks in the DNA strand
- higher effectiveness in tumors with an inactivation mutation in BRCA 1/2 gene
- Olaparib – promising results in hereditary breast cancer, ovarian cancer and prostate cancer

### Unclassified

- **Trabectedin**
  - isolated from catfish
  - demonstrated activity for soft tissue sarcomas
  - not fully understood mode of action (apparently reduces the molecular O<sub>2</sub> to form superoxide by auto-redox reaction in the vicinity of DNA, leading to irreversible damage)
- **Temsirolimus**
  - specific inhibitor of mTOR (mammalian Target Of Rapamycin) kinase, which modifies growth signals
  - excessive activation of mTOR increases the concentration of cyclin D and HIF, leading to stimulation of VEGF production
  - used in renal carcinoma, where mTOR, usually, has increased activity
- **Oblimersen**
  - bcl2 antisense oligonucleotide – blocks the production of BCL2 protein – apoptosis inhibitor
  - in clinical trials phase

## Tumor immunotherapy

Attempts to stimulate the immune system, to recognise and attack neoplastic cells:

- **administration of systemic cytokines**
  - **interferon α**
    - cytostatic to cytolytic effect
    - immunogenicity is increased by altering surface molecules
    - indications: renal cell cancer, in hematocology
  - **interleukin 2**
    - acts by activating T-lymphocytes
    - indications: renal carcinoma, malignant melanoma
- **administration of an attenuated strain of BCG** (Bacillus Calmette-Guérin) in urinary bladder carcinoma – decreased the risk of recurrence after resection
- **adoptive immunotherapy** – eg. administration of donor lymphocytes – in clinical trials phase
- **monoclonal antibodies** – see biological therapy

## Antitumor hormonal therapy

- **antiquity, middle ages** – observations: in castrated individuals there was almost no occurrence of prostate cancer
- 1896 **Beatson** first performed oophorectomy in breast cancer preventing the disease progress, which led to regression of metastatic chest wall involvement
- the oldest „biological“ (in the sense of targeted) therapy
- mostly used for malignancies derived from hormone-dependent tissue
- generally the manipulation of the endocrine system can be performed:

1. exogenous administration of **hormones**
2. by administering a substance that **inhibits** the production or activity of endogenous hormones
3. **surgical removal** of endocrine organs (oophorectomy, adnexectomy)

### Hormone synthesis inhibitors

#### Gonadotropin Releasing Hormone (GnRH)

- physiologically it stimulates the production of LH and FSH
- administration leads to chemical castration
- after a period of administration (depot form), increased LH and FSH production leads to down-regulation of LH and FSH receptors in the ovaries or in the testes, resulting in a decrease in testosterone in men and estrogen in women, leading to castration(menopausal) levels
- paradoxically, there is an increase in secretion before the onset of the effect – there is the need to administer a receptor antagonist
- goserelin – breast and prostate cancers

náhled|vpravo|400 px|Aromatase effect

### **Aromatase inhibitors (AI)**

- aromatase is an enzyme responsible for the key-step in estrogen biosynthesis – it aromatises androgens to form estrogens
- AIs competitively and reversibly inhibit aromatase
- used in post-menopausal women for receptor-positive breast cancer
- Letrozole, Anastrozole

## **Antagonists of hormonal receptors**

### **Selective modulators of estrogen receptors (SERM)**

- act on estrogen receptors
- different activity in different tissues – agonistic effect in some tissues – it depends on the co-activation and estrogen receptor conformation
- Tamoxifen
  - antagonist and agonist (eg. on endometrial mucosa – risk of hyperplasia developing into endometrial cancer)
  - indicated in hormonally positive breast cancer in both pre- and post-menopausal patients
  - biologically active only after being activated in the liver by the enzyme CYP2D6 (various isoforms, some so-called „poor metabolisers“ – amoxifen is not sufficiently effective)
- fulvestrant
  - on estrogen receptor (ER) antagonist, down-regulates and leads directly to ER degradation
  - in post-menopausal ER+ breast cancer in Tamoxifen failure

### **Antiandrogens**

- antagonists of androgen receptors
- commonly in combination with GnRH analogues or with surgical castration – the so-called complete androgen blockage
- treatment for prostate cancer
- flutamide
  - competes with testosterone DHT for the binding on androgen receptors
- bicalutamide
  - replaced flutamide because of less side effects
  - binds on the androgen receptor and accelerates its degradation

## **Other**

- some hormone receptor agonists may have anti-proliferative to cytotoxic effects

### **Gestagens - megestrol**

- not fully understood principle
- a direct effect on tumor cells and an indirect endocrine effect are expected
- 3rd line of hormonal therapy in breast, endometrial and prostate cancers

### **Androgens**

- formerly in breast cancer

### **Estrogens - diethylstilbestrol**

- suppression of testosterone production
- used in prostate cancer

### **Corticosteroids**

- not fully understood mechanism – possibly reduce uridine incorporation in RNA and with this RNA-polymerase effectivity, which leads to the reduced synthesis of RNA and proteins

- part of chemotherapeutic regimens or in monotherapy for hematological malignancies
- CLL, multiple myeloma, lymphoma
- prednisone, dexamethasone

### Somatostatin analogues

- synthetic analogues of peptide hormone somatostatin
- somatostatin inhibits the activity of some hormones adenohypophysis (GH, FSH) and production of peptide hormones in the GIT (gastrin, motilin, VIP, GIP etc.), reducing GIT secretion and motility
- used in biologically active neuroendocrine tumors – VIPoma, gastrinoma, insulinoma
- indicated in carcinoid tumor with carcinoid syndrome
- radioactive octreotide is also used in octreoscan
- octreotide (Sandostatin)

## Biological therapy (Targeted Therapy)

- blocks the growth of neoplastic cells by affecting specific molecules needed in the process of carcinogenesis, metastasis and cell growth (difference: chemotherapy „attacks“ all the rapidly dividing cells)
- mostly the whole spectrum of rather non-specific side effects of X chemotherapy

### Monoclonal antibodies („-mab“)

#### Monoclonal antibodies against tyrosine kinase receptors

- **Cetuximab** (*Erbix*)
  - chimeric (mice/human) monoclonal antibody (IgG1) against EGFR
  - expressing EGFR, KRAS wildtype (non-mutated generalised colorectal carcinoma; mCRC) and in head and neck tumors
- **Trastuzumab** (*Herceptin*)
  - human monoclonal antibody against ErbB2 (HER2/neu)
  - mechanism of action:
    - down-regulates HER2/neu, which can't dimerize and thus can't initiate signal transduction of PI3/Akt and MAPK (P27Kip1 is not phosphorylated, penetrates the nucleus and may inhibit cdk2 activity)
    - inhibit angiogenesis
    - „marks“ tumor cells for the immune system
  - used in breast cancer with over-expression of her2/neu
  - in the Czech Republic, over-expression must be proven both by immunohistochemistry (IHC +++), and by fluorescence in situ hybridisation (FISH)
  - main side effect is cardiotoxicity

#### Monoclonal antibody against other structures in solid tumors

- **Bevacizumab** (*Avastin*)
  - humanised monoclonal antibody against VEGF
  - the first clinically used inhibitor of angiogenesis
  - in combination with chemotherapy in mCRC
  - clinical trials are underway for other diagnoses without generalization
  - side effects due to angiogenesis inhibition: hypertension – risk of Stroke, ledvin damage
- **Catumaxomab**
  - binds EpCAM (epithelial cell adhesion molecule) of tumor cells with one and with the other T-lymphocyte and through its Fc-fragment another immunocompetent cell – triggering an immune reaction
  - used in therapy of malignant ascites

#### Monoclonal antibodies against other structures in leukemias and lymphomas

- **Rituximab** (*MabThera*)
  - a chimeric monoclonal antibody against CD20 found on mature B-lymphocytes (not present on plasma cells)
  - mechanism of action not fully understood (possibly a combination of several additive mechanisms)
  - used in B-lymphoma, leukemia and some autoimmune diseases
- **Alemtuzumab**
  - antibody against CD52 found on mature lymphocytes, but not on stem cells
  - 2nd line of therapy for B-CLL, T-lymphomas

- **Gemtuzumab**

- antibody against CD33, expressed on most leukemic blasts
- used in AML

## Low molecular weight inhibitors of kinases („-inib“)

- inhibit specific one or more protein kinases
- can be categorised according to the AMK, whose phosphorylation they inhibit
- most common inhibitors of tyrosine kinases
- usually „small molecules“ → penetrate biological barriers X Ig

### Receptor Tyrosine Kinase Family Inhibitors - ERB (EGFR)

- **HER1/EGFR**

- **Erlotinib** (*Tarceva*)

- reversibly binds to ATP binding site – preventing auto-phosphorylation and thus signal initiation
    - indications: NSCLC (non-small cell lung cancer) after failure of 1st line of treatment
    - with gemcitabine in generalised pancreatic cancer

- **Gefitinib**

- similar to Erlotinib; indicated in NSCLC

- **HER2/neu**

- **Lapatinib** (*Tyverb*)

- a dual inhibitor – binds on the binding site for ATP receptor tyrosine kinase in both EGFR and Her2/neu, preventing auto-phosphorylation and signal initiation
    - able to act against the so-called cancer stem cells (CSC) – they possess properties of physiological stem cells – eg. they produce all type of cells in the tumor, also, it is believed that they are responsible for relapse and metastasis of the tumor
    - indicated in the therapy of Her2/neu positive breast cancer

- **Neratinib**

### Receptor tyrosine kinase inhibitors class III

- **Sunitinib** (*Sutent*)

- inhibits several receptor tyrosine (PDGFR, VEGFR, c KIT (CD117), RET etc.)
  - indicated in renal cell carcinoma metastasis and in imatinib-resistant **gastrointestinal stromal tumor** (GIST)

- **Sorafenib** (*Nexavar*)

- inhibits several receptor tyrosine
  - the only one that blocks Raf/Mek/Erk (MAP-kinase) signalling pathways
  - in advanced or metastasized renal cell carcinoma and hepatocellular carcinoma

### Receptor tyrosine kinase inhibitors - VEGFR

- **Vandetanib** – in clinical trials for SCLC
- **Semaxanib** – in clinical trials for CRC
- **Cediranib** – in clinical trials for RCC, SCLC
- **Axitinib** – in clinical trials for pro RCC
- **Sunitinib**
- **Sorafenib**
- **Toceranib** – used in the therapy of mastocytoma
- **Regorafenib**

### Non-receptor tyrosine kinase inhibitors

- **Imatinib** (*Glivec*)

- used in GIST, CML and Dermatofibrosarcoma protuberans
  - CML with t(9;22) – Philadelphia chromosome – through translocation a fusion protein bcr-abl occurs, a constantly active tyrosine kinase, whose activity is reduced by imatinib, but it also binds on c-kit and PDGFR
  - binds on ATP binding site

