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 (effecting 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 β-subunit tubulin and thus disrupt the dynamic growth and degradation of microtubules – microtubules dont 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 β-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 glycinamide

ribonucleotide formyltransferase are also inhibited

- ***Purine analogues***
    - Pentostatin inhibits adenosine-deaminase
    - thiopurines inhibit the synthedsis 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 (CnH2n+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 *streptomycetes*
    - indication: HD, testicular cancer
    - Mitomycin – a product of *streptomycetes*
        - 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 hereditaty 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_2 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***
    - blc2 antisense oligonukleotide – 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 hematooncology
    - ***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 oopherectomy in breast cancer preventing the disease progress, which lead 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 (oopherectomy, 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

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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*** (*Erbitux*)
    - 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-lymhomas

- ***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 posses 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 **g**astro**i**ntestinal **s**stromal **t**umor (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

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