Antitumor therapy

Biochemical principles of antitumor treatment

Antitumor Treatment Modalities

Local treatment:

- surgery
- radiotherapy

Systemic therapy:

- chemotherapy
- immunotherapy
- hormonal treatment
- biological therapy

Criteria for the choice of modality and type of drug:

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

Chemotherapy

- development after World War I, when nitrogen mustard mustard (alkylating agent) was used for the first time
- by interfering with the cell cycle tumor cells prevent their further division
- the most sensitive are rapidly proliferating cells and cells that have a reduced ability to repair DNA errors
- acts non-specifically, which leads to the characteristic **undesired effects** of the treatment (effect on physiologically rapidly dividing cells):
    - temporary suppression of blood formation (hematopoietic cells of the bone marrow)
    - GIT problems (mucosal cells of the alimentary canal)
    - alopecia (hair follicle cells) and others

Division by mechanism of action

🔎 *For more information see Cytostatics.*

Mitosis inhibitors

Vinca alkaloids ("mitotic poisons") – Vinblastine, Vincristine, Vinorelbine

- alkaloids of periwinkle, synthetically produced in use today
- they bind to the β-subunit of tubulin and thus disrupt the dynamics of growth and degradation of microtubules - there is no polymerization of microtubules (they depolymerize directly at increased concentrations)
- Indications: breast cancer, lung and others

Taxanes - Docetaxel, Paclitaxel

- chemically diterpenes
- originally from Pacific yew (paclitaxel), now produced synthetically
- by binding to the β-unit of polymerized tubulin, they increase the affinity of tubulin units to each other - stabilization of the microtubules of the dividing spindle - stopping of mitosis during the transition from metaphase to anaphase
- indication: breast cancer, ovarian cancer, prostate cancer 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, in addition to DHFR it also inhibits thymidylate synthase and glycinamide ribonucleotide formyltransferase

- ***Purine analogs***
    - Pentostatin inhibits adenosine deaminase
    - thiopurines inhibit the synthesis and metabolism of purines (Mercaptopurine)
- ***Pyrimidine analogs***
    - inhibit thymidylate synthase (5-FU, Capecitabine) – cancers of the GIT, breast etc.
    - inhibit DNA-polymerase
    - inhibit ribonucleotide reductases (Gemcitabine) – pancreatic cancer
    - inhibit DNA methylation
- ***Ribonucleotide reductase inhibitors***
    - Hydroxyurea – in myeloproliferative diseases

Topoisomerase Inhibitors'

- ***Topoisomerase I inhibitors***
    - topotecan – ovarian cancer + SCLC
    - irinotecan – colon cancer
- ***Topoisomerase II inhibitors***
    - etoposide - lung cancer, testicular tumors and others
- ***Topoisomerase II inhibitors with intercalation activity***
    - **anthracyclines'** = anthracycline ATB
    - produced by strains of bacteria *Streptomyces*
    - in addition to inhibiting topoisomerase II, it also acts as an intercalator (they are inserted between two DNA strands)
    - Doxorubicin, Epirubicin – cancer of the breast, ovaries, hematological malignancies

Substances acting by an alkylating or intercalating mechanism'

- ***Drugs acting through an alkylating mechanism***
    - alkylating agents: transferring an alkyl group (CnH2n+1) to N7 of the imidazole ring guanineu
    - cyclophosphamide – hematological malignancies
- ***Platinum cytostatics***
    - do not alkylate in the true sense of the word - they do not have an alkyl group - only a similar effect to alkylating agents
    - bind with DNA to form intercalation bonds that prevent replication and repair processes
    - CDDP (cisplatin), oxaliplatin, CBDCA (carboplatin) – the basis of combined chemotherapy regimens for many solid tumors (sarcomas, ovarian cancer, lung cancer)
- ***Non-classical alkylating agents***
    - Dacarbazine – malignant melanoma, hematological malignancies
    - Temozolomide – glioblastoma G IV
- ***Alkylating and intercalating substances***
    - Bleomycin – glycopeptide ATB produced by ``streptomycetes
    - indication: HD, testicular tumors
    - Mitomycin – a "streptomycete" product
        - breast cancer, bladder cancer

Enzyme inhibitors

Inhibitors of farnesyl transferase – Tipifarnib

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

Inhibitors of cyclin-dependent kinases (CDKi) – Seliciclib

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

proteasome inhibitors – Bortezomib

- proteasome inhibitor (inhibits its chymotrypsin-like proteolytic activity)
- leads to cell cycle arrest by stabilizing negative cell cycle regulators (proapoptotic proteins are not degraded, leading to induction of apoptosis)
- proven efficacy in Multiple Myeloma and Mantle Cell Lymphoma

PARP inhibitors (Poly ADP Ribose Polymerase inhibitors)

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

Uncategorized

- ***Trabectidine***
    - isolated from catfish
    - efficacy demonstrated for soft tissue sarcomas
    - mechanism of action not fully clarified (apparently reduces molecular O_2 to form superoxide by an auto-redox process near DNA, which leads to irreversible damage)
- ***Tensirolimus***
    - a specific mTOR (mammalian Target Of Rapamycin) kinase inhibitor that modifies pro-growth signals
    - with excessive activation of mTOR, there is an increase in the concentration of cyclin D and HIF, which leads to the stimulation of VEGF production
    - in renal carcinoma, where mTOR often has increased activity
- ***Oblimersen***
    - blc2 antisense oligonucleotide - blocks the production of the BCL2 protein - an inhibitor of apoptosis
    - in the clinical research phase

Antitumor immunotherapy

Trying to stimulate the immune system to recognize and destroy tumor cells:

- **by administering systemic cytokines**
    - ***interferon α***
        - cytostatic to cytolytic effect
        - changes in surface molecules lead to an increase in immunogenicity
        - indication: generalized kidney cancer, in hemato-oncology
    - ***interleukin 2***
        - has an activating effect on T-lymphocytes
        - indication: kidney cancer, malignant melanoma
- **administering an attenuated strain of BCG** (Bacillus Calmette-Guérin) in bladder cancer - reduces the risk of disease recurrence after resection
- **adoptive immunotherapy** - eg administration of donor lymphocytes - in the clinical research phase
- **monoclonal antibodies'** - see biological therapy

Antitumor hormone therapy

- **ancient times, middle ages'** - observation: castrates had almost no prostate cancers
- 1896 **Beatson** was the first to perform ovariectomy for breast cancer to stop the progression of the disease, leading to regression of metastatic involvement of the chest wall
- the oldest "biological" in the sense of targeted therapy
- mostly used for malignancies derived from hormone-dependent tissue
- in general, manipulation of the endocrine system can do:

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

Inhibition of hormone synthesis

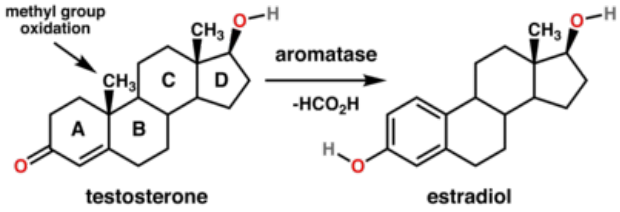
Gonadotropin Releasing Hormone (GnRH)

- stimulates the production of LH and FSH in the body
- administration leads to chemical castration
- after a certain period of administration (depot form) the increased production of LH and FSH leads to the

down-regulation of receptors for LH and FSH in the ovaries or testes, which results in a decrease in testosterone in men and estrogens in women to the castration (menopausal) level
- before the onset of the effect, there will paradoxically be an increase in secretion - the need to administer a receptor antagonist
- goserelin – breast and prostate cancer

Aromatase inhibitors (AIs)

- aromatase (AR) is an enzyme responsible for a key step in estrogen biosynthesis – it aromatizes androgens to form estrogens
- AIs competitively and reversibly inhibit ARs
- are used in postmenopausal women with receptor-positive breast cancers
- letrozole, anastrozole



Hormone receptor antagonists

Selective Estrogen Receptor Modulators (SERMs)

- acts on the estrogen receptor
- different activity in different tissues - agonistic effects in some tissues - depends on coactivators and conformation of estrogen receptor
- tamoxifen
  - both antagonist and agonist (e.g. on the endometrial mucosa – risk of hyperplasia up to endometrial cancer)
  - indicated for hormone-positive breast cancers in pre- and postmenopausal patients
  - biologically active only after activation in the liver parenchyma by the enzyme CYP2D6 (various isoforms, some so-called "bad metabolizers" - tamoxifen is then not effective enough)
- fulvestrant
  - only estrogen receptor (ER) antagonist, down-regulates and leads directly to ER degradation
  - in postmenopausal ER+ ca breasts with tamoxifen failure

Antiandrogens

- androgen receptor antagonists
- often in combination with GnRH analogues or with surgical castration – so-called total androgen blockade
- prostate cancer treatment
- flutamide
  - competes with testosterone and DHT for binding to the androgen receptor
- bicalutamide
  - replaced flutamide for less intensity of side effects
  - binds to the androgen receptor and accelerates its degradation

Others

- some hormone receptor agonists can have an antiproliferative or cytotoxic effect

Progestogens – megestrol

- the principle is not fully clarified
- a direct effect on tumor cells and an indirect endocrine effect are assumed
- III. line of hormone therapy ca mammy, endometrium and prostate

Androgens

- previously at ca mom's

Estrogens - diethylstilbestrol

- suppression of testosterone production
- in prostate cancer

Corticosteroids

- the mechanism is not fully understood - they probably reduce the incorporation of uridine into RNA and thereby the effectiveness of RNA polymerase, which ultimately leads to a reduction in RNA and protein synthesis
- part of chemotherapy regimens or in monotherapy for hemato-oncological malignancies
- CLL, multiple myeloma, lymphomas
- prednisone, dexamethasone

Somatostatin analogs

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

Biological treatment (targeted therapy)

- blocks the growth of tumor cells by affecting specific molecules important in the process of carcinogenesis, metastasis and cell growth (difference: classical chemotherapy "attacks" all rapidly dividing cells)
- usually the whole spectrum of rather non-specific side effects of X chemotherapy

Monoclonal antibodies ("-mab")

Monoclonal antibodies against tyrosine kinase receptors

- ***Cetuximab*** (*Erbitux*)
    - chimeric (mouse/human) monoclonal antibody (IgG1) against EGFR
    - in EGFR expressing, KRAS wildtype (unmutated generalized colorectal carcinomas; mCRC) and in head and neck carcinoma
- ***Trastuzumab*** (*Herceptin*)
    - human monoclonal antibody against ErbB2 (HER2/neu)
    - mechanisms of action:
        - downregulates HER2/neu, which cannot dimerize and thus does not initiate the PI3/Akt and MAPK signaling pathway (P27Kip1 is not phosphorylated, enters the nucleus and can inhibit cdk2 activity)
        - inhibits angiogenesis
        - "marks" tumor cells for the immune system
    - in breast cancer with her2/neu overexpression
    - in the Czech Republic, overexpression must be proven both by immunohistochemistry (IHC +++) and by fluorescence in situ hybridization (FISH)
    - the main adverse effect is cardiotoxicity

Monoclonal antibodies against other structures in solid tumors

- ***Bevacizumab*** (*Avastin*)
    - humanized monoclonal antibody against VEGF
    - the first clinically used angiogenesis inhibitor
    - in combination with chemotherapy in mCRC
    - clinical studies for other diagnoses are ongoing even without generalization
    - side effects from inhibition of angiogenesis: hypertension - risk of CMP, kidney damage
- ***Catumaxomab***
    - binds EpCAM (epithelial cell adhesion molecule) to tumor cells with one arm and with the other T-lymphocyte and another immunocompetent cell with an Fc fragment - triggers an immune reaction
    - used in the therapy of malignant ascites

Monoclonal antibodies against other structures in leukemias and lymphomas

- ***Rituximab*** (*MabThera*)
    - chimeric monoclonal antibody against CD20 protein found on maturing B-lymphocytes (no longer on plasma cells)
    - mechanism of action not entirely clear (probably a combination of several additive mechanisms)
    - treatment of B-lymphomas, leukemias and some autoimmune diseases
- ***Alemtuzumab***
    - antibody to CD52 is found on mature lymphocytes but not on stem cells
    - second-line therapy in B-CLL, T-lymphomas
- ***Gemtuzumab***
    - antibody against CD33, expressed on most leukemic blasts
    - in AML

Small molecule inhibitors of kinases ("-inib")

- inhibit specifically one or more protein kinases
- can be categorized according to the AMK whose phosphorylation they inhibit
- most often tyrosine kinase inhibitors
- mostly "small molecules" → penetrate biological barriers well X Ig

Inhibitors of the receptor tyrosine kinase family - ERB (EGFR)

- **HER1/EGFR'**
    - ***Erlotinib*** (*Tarceva*)
        - binds reversibly to the binding site for ATP – prevents autophosphorylation and thus signal initiation
        - indication: NSCLC (non-small cell lung cancer) after failure of at least 1 line of CHT
        - with gemcitabine in generalized pancreatic cancer
    - ***Gefitinib***
        - similar to Erlotinib; indicated in NSCLC
- ***HER2/neu***
    - ***Lapatinib*** (*Tyverb*)
        - is a dual inhibitor – it binds to the binding site for ATP receptor tyrosine kinases in both EGFR and Her2/neu and thus prevents autophosphorylation and signal initiation
        - able to act against so-called tumor stem cells (cancer stem cells, CSC) – they have the properties of normal stem cells – e.g. produce all types of cells in the tumor, it is assumed that they are responsible for relapses and metastases
        - indicated for the therapy of Her2/neu overexpressed breast Ca
    - ***Neratinib***

Inhibitors of receptor tyrosine kinases of class III

- ***Sunitinib*** (*Sutent*)
    - inhibits several receptor tyrosine kinases (PDGFR, VEGFR, c KIT (CD117), RET etc.)
    - indicated in metastatic renal cell carcinoma and in imitanib-resistant **g**astro**i**ntestinal **s**tromal **t**tumors (GIST)
- ***Sorafenib*** (*Nexavar*)
    - inhibits several receptor tyrosine kinases
    - is unique in blocking the Raf/Mek/Erk (MAP-kinase) signaling pathway
    - in advanced or metastatic renal cancer and hepatocellular carcinoma

Inhibitors of receptor tyrosine kinases - VEGFR

- ***Vandetanib*** - in clinical trials for SCLC
- ***Semaxanib*** - in the phase of clinical trials for CRC
- ***Cediranib*** - in the phase of clinical trials for RCC, SCLC
- ***Axitinib'*** - *in the phase of clinical trials for RCC*
- ***Sunitinib***
- ***Sorafenib***
- ***Toceranib*** - used for therapy mastocytomas
- ***Regorafenib***

Inhibitors of non-receptor tyrosine kinases

- ***Imatinib*** (*Glivec*)
    - in GIST, CML and dermatofibrosarcoma protuberans
    - CML with t(9;22) - Philadelphia chromosome - translocation produces a fusion protein bcr-abl, which is a constantly active tyrosine kinase whose activity is reduced by imatinib, but also binds to c-kit and PDGFR
    - binds to the ATP binding site

Links

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