Anticancer therapy (1)
Tumor epidemiology

Major death cases: year 2001 ÚZIS

1. Cardiovascular diseases 53%
2. Cancer 26%
3. Injuries, intoxication 6%
4. Respiratory diseases 4%
5. GI diseases 4%
6. Others

Death according to cancer: year 2001 ÚZIS

1. Lung cancer 33,8%
2. Colorectal cancer 23,7%
3. Breast cancer 11,0%
4. Gastric cancer 8,3%
5. Pancreas 8,1%
6. Kidney 6,3%
7. Prostate 6,2%
8. Ovarian 4,1%
9. Uterus 2,4%

Oncology reporting is mandatory
Cell cycle

Synthesis of cell components essential for mitosis

replication
DNA (synthesis)

Synthesis of cell components essential for DNA synthesis

g2
19%

G1
39%

S
39%

G2
19%

synthesis of cell components essential for DNA synthesis

M
mitosis

differentiation

G0

Cell cycle regulation:
Positive – cyclines, CDK a growth factors, negative – pRb, p53
Cell cycle and role of cyclines and CDK

- G1
- S
- G2
- M

Cyclin D1
- CDK 2

Cycline B
- CDK 1

Cycline A
- CDK 2

Cycline E
- CDK 2

Dephosphorylation
- pRb, p53

Stimulation by means of growth factors

G0

Phosphorylation
- pRb
Tumor growth

- Tumor growth is cell proliferation out of growth control, in comparison with healthy tissues:
  - Uncontrolled proliferation
  - Dedifferentiation and loss of function
  - Invasivity
  - Metastases

- Tumor growth as an alteration of:
  - Growth factors function
  - Cyclines and CDK function
  - DNA synthesis and increase of oncogen expression
  - Influence of negative regulation in relation to mutations and suppressor gens
Tumor growth (II)

• Mechanism of uncontrolled proliferation
  – Extracellular signals (oncogens) e.g. growth factors
    • Platelet derived growth factor – PDGF
    • Vascular endothelial growth factor – VEGF
    • Epidermal growth factor – EGF
  – Receptors (cell membrane) e.g.
    • \textit{c-erb} – epidermal growth factor EGF/EGFR
  – Intracellular signal transduction e.g.
    • Cytosolic – proto-oncogene \textit{ras}
    • Nuclear – proto-oncogene \textit{c-myc} transduction = stimulation of multiple cell division.
  – Cell cycle
    • Cycline and CDK production
TK receptor family and their activation

**HER (erbB) Family**
- TGF-α
- EGF
- None
- Heregulin
- Epiregulin
- Heregulin
- Epiregulin
- EGFR
- HER2
- HER3
- HER4

**VEGFR Family**
- VEGF-A
- VEGF-B
- VEGF-A
- VEGF-C
- VEGF-D
- VEGF-C
- VEGF-D
- VEGFR-1
- VEGFR-2
- VEGFR-3
- VEGFR-1
- VEGFR-2
- VEGFR-3

**PDGFR Family**
- FL
- PDGF
- SCF
- Flt-3
- PDGFR
- KIT

**Receptor Dimerization and Activation**
- IGF-1R
- VEGFRs, PDGFR, KIT, Flt-3
- EGFR/HER2
- Mutant Flt-3
Antitumor therapy

- Cytostatics
- Hormones and antihormones
- Retinoids and other inducers of differentiation
- *Bio therapeutics*
- Inhibitors osteolysis
- Antidotes and protectives
- Supportive therapy
Classification of cytostatics

- Category
  - Antimetabolites
  - Alkylating agents
  - Antitumor antibiotics
  - Alkaloids of plant origin
  - Others
Classification of cytostatics

According to Cell cycle alteration

Phase specific
Vinca-alkaloids – mitosis
Hydroxyurea, MTX, Ara-c – S-phase
5-FU – G1 a S-phase

Cycle specific
Alkylating agents, doxorubicin, DDP – all cycle around

Cycle non-specific
Bleomycin, nitrosoureas – cycle independent
Cytostatics and cell cycle

- **G0**
  - G0

- **G1**
  - Vincristine (HD)
  - Prednizon
  - Actinomycin D
  - (carmustine) BCNU
  - Alkylating agents

- **S**
  - 6-Mercaptopurine
  - Methotrexate
  - 5-Fluorouracil

- **G2**
  - Tenopozide
  - Vincristine
  - Vinblastine
  - Colchicine

- **M**
  - diferenciación

- **Alkylating agents**
  - Hydroxyurea
  - Mitomycin C
  - Cytarabine (Ara-C)

- **Antitumor antibiotics**
  - Tenopozide
  - Vincristine
  - Vinblastine
  - Colchicine
Mode of action of cytostatics

- Inhibition of nucleic acid synthesis
- Damage of nucleic acid
- Alteration microtubular protein (spindle poisons)
- Proteosynthethic inhibitors
- Cell membrane damage
- Combined effects
Antimetabolites

• Inhibition of nucleic acid synthesis
  – Direct inhibition (level of intermediary metabolism)
  – Incorporation of antimetabolites (false NA chains)
  – Inhibition of metabolism (feed back mechanism)
  – Classification of antimetabolites according to substrates
Antimetabolites

- Antifolates (dihydrofolate reductase inhibition)
- Antipyrimidines
  - Uracil – fluorinated pyrimdines (5-Fluorouracil)
- Antipurines
  - Guanin – hypoxantin
  - Adenin – adenosin
- Ribonucleosid reductase inhibitors
  - hydroxyurea
Antimetabolites - Antifolates

- Methotrexate (MTX)
- Trimethotrexate

- Dihydrofolate reductase inhibition = dihyhydrofolic acid cannot be reduced to tetrahydrofolic acid.
- Active transport into the cells
- Tumor cells with altered transport mechanism are resistant
- HD MTX – passive transport (overcome the resistance)
Antimetabolites - Antipyrimidines

- 5-fluorouracil (5-FU)
  - Regimes (examples):
    - FOLFIRI – 5-FU + Folic acid + Irinotecan (breast)
    - FOLFOX – 5-FU + Folic acid + Oxaliplatin (breast)
    - IFL – 5-FU + Irinotecan (solid tumors)

- Cytarabine (Ara-C)
- Gemcitabine
- Capecitabine

5-FU → 5-FUMP → FUTP and/or FdUMP

1. FUTP – incorporation into DNA = alteration
2. FdUMP (fluorodeoxyuridin monophosphate) thymidylate synthethase inhibition = disruption of DNA synthesis

- MTX potentiates effect of antipyrimidines
Antimetabolites - Antipurines

- 6-Mercaptopurine
- Thioguanine
- Azathioprine

1. De novo purine synthesis inhibition
2. False precursor – nucleotidetriphosphate
Antimetabolites - Antipurines

- Adenosine analogue
  - Fludarabine
  - Cladribine
Antimetabolites - ribonucleotid reductase inhibitors

- Hydroxyurea
- Diarylsulfonylurea

  - Structurally not related to nucleotide precursors

1. Ribonucleotid reductase inhibition = disruption in DNA synthesis
2. Disruption of reparation altered DNA
Alkylating agents

- Mechlorethamine
  - Regime MOPP: Non-Hodgkin's lymphoma
    (mechlorethamine – vincristine/oncovine – prednisone – procarbazine)
- Chlorambucil
- Melphalan
- Oxaphosphorines
- Nitrosoureas
- Busulfan
- Estramustine
- Tetrazines
- Non-classified
Alkylating agents

- Alteration of structure and function of nucleic acid – inhibition of replication, transcription, translation

  - Alkylation
    - Simple substitution (substitution of base e.g. N\textsubscript{7} guanine or phosphate esterification)
    - Bi-functional substitution – necessity of 2 radicals (groups) capable to react between neighboring guanines of the same or parallel (neighboring) chains
    - Other mode of action – depurination and split of the DNA (radiomimetic effect)
    - Resistance mechanisms
      - Increased endonuclease production (reparation of altered DNA)
      - Increased contents of proteins with SH groups binding alkylation agents
      - Differences in transport mechanisms and properties functional group
Alkylating agents - Oxaphosphoranes

- Cyclophosphamide
  - Regimen CHOP (cyclophosphamide + doxorubicine + vincristine/o + prednisone – NHL, B-CLL)
- Iphosphamide
- Maphosphamid
Alkylating agents - nitrosoureas

- Carmustine (BCNU)
- Lomustine (CCNU)
- Streptozocine
Alkylating agents - Tetrazines

- Dacarbazine (DTIC)
  - Combined mode of action (alkylation agent + purine antimetabolite)
- Temozolomide
Procarbazine
  – Atypical alkylating agent
Antitumor antibiotics

- Antracyclines
- Drugs related to antracyclines
- Bleomycin
- Mitomycin C
- Dactinomycin
Antracyclines – Antitumor antibiotics

- Alteration of structure and function of nucleic acid – inhibition of replication, transcription, translation
  - Intercalation (*vmezeření, vsuvka in Czech*)
    - No covalent link (cytostatic – DNA)
  - **Topoizomerase II inhibition**
  - Cell membrane alteration
  - Formation of **oxygen radicals** (superoxides and peroxides)
    - Outcome – antracycline cardio toxicity
Antracyclines – Antitumor antibiotics

• Doxorubicine
  – Pegylated liposomal doxorubicine (*CAELYX*)
• Daunorubicin
• Idarubicine
• Epirubicine
• Related compounds - Mitoxantrone
Bleomycin - Antitumor antibiotics

- Alteration of structure and function of nucleic acid – inhibition of replication, transcription, translation
  - Split of DNA molecule (radiomimetic effect)
    - **Disruption** on one or both DNA chains
    - Formation of **oxygen radicals** (superoxides and peroxides)
    - Ligase inhibition disable reparation of altered chains
      - Decreased amino peptidase concentration results in lung and skin alteration
Alkaloids of plant origin

- Vinca-alkaloids
- Taxanes
- Camptotecine analogues
- Podophylotoxine alkaloids
Alkaloids of plant origin

• Alteration of microtubular protein (spindle poison)
  – Inhibition of polymeration (colchicin, vinca-alkaloids) disruption of mitosis in metaphase
  – Inhibition of depolymeration (taxanes) accelerates formation of microtubules

  – Outcome of both mechanisms same – alteration of mitosis
Microtubules – outcome of targeted antitumor therapy

- Microtubule
- Microtubule Dynamics
- Depolymerization
- Polymerization
- Mitosis
- G1
- G2
- S
- Cell Death
- Microtubule Stabilizer
Alkaloids of plant origin – Vinca-alkaloids

- Vincristine
- Vinblastine
- Vindesin
- Vinorelbine (i.v./oral)

- Outcome of inhibition – irregular distribution of chromosomes (explosive metaphasis)
- Vinca-alkaloids reveal as well antimetabolic effect and RNA-polymerase inhibition
Alkaloids of plant origin - Taxanes

- Paclitaxel
- Docetaxel (higher affinity to microtubules)
  - Altered microtubules bundles and/or non-functional formations (pseudo asters) – mitosis is extended from 30 min to 15 hrs.
  - Taxanes disrupt transition from $G_2$ to $M$ phase – radiopotentiation effect on cells in most sensitive phase
  - Apoptotic inducer
Alkaloids of plant origin - Camptotecin

- Alteration of structure and function of nucleic acid – inhibition of replication, transcription, translation
  
  - **Topoizomerase I**, inhibition – single strand breaks in DNA
  - Topoizomeraseases - enzymes, supporting changes in sterical configuration during DNA replication
    Topoizomerase I inhibitors do not reveal MDR (multidrug resistance)
Topoisomerase I inhibition induces DNA breaks and cell death

- Replication fork encounters stabilized Topo I DNA complex
- Replication stops
- DNA single-strand breaks
- Cell death
Alkaloids of plant origin - Camptotecin

- Irinotecan – regime: IROX, IFL (solid tumors)
- Topotecan
Alkaloids of plant origin - Podofylotoxin

Alteration of structure and function of nucleic acid – inhibition of replication, transcription, translation

- **Topoizomerase II inhibition**
- Antitumor effect only in sufficient dose – repeated dosage needed
Alkaloids of plant origin - Podofylotoxin

- Etoposide
- Tenoposide
Non-classified cytostatics

- Platinum cytostatics
  - Mode of action similar to alkylating agents
    alteration and inhibition of DNA synthesis
  - Initiate intercalation bonds between DNA chains
- Non-essential amino acids
  - L-asparaginase – proteosynthetic inhibitor results
    L-asparagine depletion. Resistance based on L-
    asparaginsynthetethase excessive production
Platinum cytostatics

- Cisplatin (DDP)
- Carboplatin
- Oxaliplatin – regimes: FOLFOX, IROX (solid tumors)
Adverse effects of cytostatics

- **Immediate** – hrs-days
  - Nausea, vomitus, renal insufficiency, rash, local reactions

- **Early** – days-weeks
  - Leucopenia, thrombocytopenia, alopecia, stomatitis

- **Delayed** – weeks-months
  - Anemia, pulmonary fibrosis, hyper pigmentation

- **Late** – months-years
  - Sterility, hypogonadism, secondary malignancies
Evaluation of toxicity according to WHO a CTC NCI

- Toxicity grades 0 – 4
  0 – None / normal status
  1 – Mild
  2 – moderate
  3 – Pronounced
  4 – Severe / irreversible / life threatening

CTC = Common Toxicity Criteria
Frequency of AE

- 1/10  Very frequent
  - neutropenia, thrombocytopenia, anemia, alopecia, vomitus
- 1/100  Frequent
- 1/1000  Less frequent
- 1/10000  Rare
- 1/100000  Very rare
Adverse effects of cytostatics

- **Hemopoiesis**
  - Myelosuppression, granulocytopenia, thrombocytopenia, anemia – majority of cytostatics

- **GI**
  - Malabsorption, diarrhea
  - **Nausea and vomiting**
    - Very strong emetogen: cisplatin, cyclophosphamid
    - Strong emetogen: carboplatin, doxorubicin
    - Moderate emetogen: etoposid, methothreat
    - Mild emetogen: busulfan, cyclophosphamid
      p.o.
Adverse effects of cytostatics

- **Skin and soft tissues**
  - Pigmentation, cellulites, alopecia, palmo-plantar erytema
  - Alopecia

- **Cardiotoxicity**
  - Arrhythmias, bradycardia – antracyclines, paclitaxel

- **Lung toxicity**
  - Interstitial lung fibrosis – bleomycin

- **Nefrotoxicity**
  - cisplatin

- **Neurotoxicity**

- **Reproductive organ toxicity**

- **Ocular toxicity** – cataracta (busulfan)

- **Teratogenity**
<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicity</th>
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<tbody>
<tr>
<td>Carboplatin</td>
<td>trombocytopenia</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>peripheral neuropathy, nefrotoxicity</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>peripheral neuropathy</td>
</tr>
<tr>
<td>Etoposid p.o.</td>
<td>secondary leukemia, myelosupression</td>
</tr>
<tr>
<td>Vinorelbin</td>
<td>leucopenia</td>
</tr>
<tr>
<td>Taxotere</td>
<td>liquid retention</td>
</tr>
<tr>
<td>Ifosfamid</td>
<td>leucopenia, anemia, nefrotoxicity</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>hand-foot syndrome</td>
</tr>
</tbody>
</table>
Mechanisms of resistance to cytostatics

- **Primary resistance** – tumor a priori resistant
- **Secondary resistance** – acquired

- Increased efflux
  - Cytostatics (MDR)
  - Transmembrane P-glykoprotein (doxorubicin, vinblastine…)

- Decreased penetration of cytostatic
  - MTX
  - Increased intracellular link of cytostatic (glutathionový systém)

- Increased metabolic turnover of cytostatic to inactive metabolite
  - (5-FU, ara-C)

- Decreased metabolic turnover inactive to active compound
  - (ara-C)

- Alteration of specific target enzymes (e.g. DHFR u resistance to MTX)
  - Increased intensity of reparation DNA (alkylating agents)

- Change in intracellular distribution of cytostatic (e.g. to lysozomes)
  - Alteration of specific target enzymes (topoizomerse II – doxorubicin)
Handling of cytostatics

• Cytotoxic, mutagenic and cancerogenenic substances – special hygienic regulations

• SOPs for handling with cytostatics

• Special working compartment

• Prevention of contamination and rules of decontamination
General rules of rational chemotherapy

Cyclic application and intervals
Specific rules for different cytostatics and tumors

• Initiate treatment asap.
• Combine more drugs to increase outcome
• Sufficient high doses
• Optimum application intervals
• Optimum intervals between cycles
• Fight residual disease after clinical remission
# General rules of rational chemotherapy

<table>
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<th>First choice</th>
<th>Second choice</th>
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<td>Broad spectrum cytostatics</td>
<td>Low toxicity cytostatics</td>
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<tr>
<td>Antracyklines</td>
<td>Hydroxyurea</td>
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<tr>
<td>Cyclophosphamide</td>
<td>Cytarabine</td>
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<tr>
<td>Nitrosourea</td>
<td>Mercaptopurin</td>
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<tr>
<td>Cisplatin</td>
<td>Novel compounds</td>
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<td>Narrow spectrum cytostatics</td>
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<td>Narrow spectrum cytostatics</td>
<td>Cytostatics with narrow therapeutic index</td>
</tr>
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<td>Novel compounds</td>
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</tr>
</tbody>
</table>
Treatment of progressive disease

- Pretreatment e.g. platinum (1st line)
- Remission
- 2nd line chemotherapy
- Remission
- 3rd line chemotherapy
• Induction th: – first aggressive therapy – outcome = remission (HD therapy, several cycles, AEs)
• Consolidation th: new combination to fight with resistant cells
• Re-induction th: residual disease management
• Maintenance th: dubious (small doses to prevent relapse)
Application of cytostatics(II)

• Neoadjuvant – prior surgery or irradiation
  – To reduce tumor mass

• Adjuvant – complementary to basic therapy e.g. surgery
  – Cure residual disease
Influence of chemotherapy on tumor cell population

Number of tumor cells $10^n$

- CH
- CH
- CH
- CH
- CH
- CH

- a = relaps after treatment
- b = treatment delayed relaps
- c = cured

lethal borderline

remission

relaps

cured

time
Therapy in oncology (I)

• Complex approach – palliative/curative

• Surgery

• Radiotherapy
  – External irradiation
  – Internal irradiation
  – Intraperitoneal (cave irregular distribution!)

• Cytostatics

• Immunotherapy, cytokines, imunotoxins, monoclonal antibodies
Therapy in oncology (II)

- Systemic therapy:
  - cytostatics - chemotherapy - cytotoxic nonselective effect
  - hormonal - breast, endometrial and prostate carcinomas - antiestrogen-tamoxifen

- Pain management, symptomatic therapy

**Survival length and QoL**

*KPI (Karnofsky Performance Index 100 – 0) and WHO scale 0 – 4*
Evaluation of therapeutic effect

- Extend of tumor reduction
- Duration of response
- Survival rate
- Toxicity

**Objective response (OR)**
- Measurable disease (WHO) – Change in sum of 2 largest rectangular diameters
- Target lesions (NCI – RECIST) – Change in sum of largest diameter 5/organ 10/total

- Non-measurable lesions
  - Intraabdominal, spinal, bone or diffuse brain metastatic lesions

RECIST = Response Evaluation Criteria in Solid Tumors
Objective response (OR) evaluation (RECIST/WHO)

• Complete Response **CR** – Disappearance of measurable signs of disease documented during control as minimum after 4 weeks

• Partial Response **PR** – Decrease of measurable signs 30% and more documented during control as minimum after 4 weeks

• (WHO dtto, but 50%)

• Stable Disease **SD** – Does not fit into criteria for PR or PD. (WHO – no change NC)

• Progressive Disease **PD** – tumor growth or increase of measurable changes 20% more vs. least sum or new lesion (WHO 25% in 1 or more lesions or new lesion)
Evaluation of duration of response

• Disease free interval **DFI**
  – From complete remission first signs of relapse (patients in complete remission)

• Time to progression **TTP**
  – From initiation of the therapy to the progression (patients in PR, CR, NC)

• Overall survival **OS**
  – From first therapy (resp. first diagnosis) and death – surviving patients are *censored* to the date of last visit

  • Event = událost (úmrtí, relaps, progrese…)
  • Time to event
  • Follow up (další sledování)
Hormones and antihormones

- Estrogens
- Antiestrogens
- Progesterone
- Aromatase inhibitors
- Androgens
- Antiandrogens
- Corticosteroids
- Gonadorelin antagonists
- Others
Mode of action of steroid hormones

1. Change in cell function
2. New receptor protein

*GRE is encoded: GGTACA nnn TGTTCT
Estrogens – Antiestrogens – Progesterons

• Estrogens
  – Polyestradiol
  – Estramustine
    • Ca prostate

• Antiestrogens – (Selective Estrogen Receptor Modulator – SERM)
  – Tamoxifen
  – Fulvestrant
  – Raloxifen
    • Disrupt link if estrogen on the level of ERE (estrogen response element)
    • Proteinkinase C inhibitors

• Progesterons
  – Megestrol
  – Medroxyprogesteron acetat
    • Endometrial Ca, Progesteron decrease number of estrogen receptors
Aromatase inhibitors

- Steroid
  - Exemestan

- Non-steroid
  - Aminoglutetimide
  - Formestan
  - Anastrozol
  - Letrozol

- Aromatases convert androstendione and testosterone to estrone and estradiol in suprarenal gland
- Inhibition = medicamentous adrenalectomy
Androgens - Antiandrogens

- Androgens
  - Testosterone propionate
    - Breast cancer

- Antiandrogens
  - Cyproteron acetat
  - Nilutamid
  - Bikalutamid
  - Flutamid
    - Prevent by competitive inhibition to link testosterone and dihydrotestosterone on cellular receptors
Glucocorticoids

- Prednisone
- Dexamethasone

- Inhibition of uridine entry into NA by decreasing of RNA-polymerase activity
- Induce apoptosis in lymphocytes
Gonadoliberin agonists

- Gosrelin
- Leuprolin
- Triptorelin

Gonadoliberins (LH a FSH)
- In physiological dose control gonad function
- In pharmacological dose suppress gonadotrophin release = pharmacological castration
Retinoids and other differentiation inducers

- Tretinoin
- Izotretinoin
- Etretinate
- Vitamin D₃
- Selective agonists of retinoid receptors

- Deltanoids
Anticancer therapy (2)
Biological therapy and regulatory peptides

- Interleukins
- Hemopoietic growth factor
- Interferons
- Monoclonal antibodies
- Small molecules interfering with intracellular signal transduction
Interleukines – Imunomodulation cytokines

- IL-1 – ...
- IL-2 – T-cell growth factor (*Aldesleukin - Proleukin*) Receptor IL-2R transduce signal trigger by means of activation pathways:
  - **A.** Mitogen Activated Protein Kinase cascade (MAPK): outcome = cell proliferation
  - **B.** fosfatidil-inositol-3 kinase pathway influencing changes in cytoskeleton
  - **C.** activation of Janus kinase (JAK1 a JAK3)
- …IL-18…
Interleukin 2 (Aldesleukin)

• Indication
  – in combination: 5-FU + IFNα + IL-2 (RCC) - 1. line
  – Melanoblastoma

• Adverse events
  – Capillary leak syndrome – hypotension, edema
    intravascular hypovolemia
  – Nefrotoxicity
Interleukin 2 (Aldesleukin) and signal transduction
Hemopoetic growth factors (I)

- **Leukocyte growth factors**
  - Filgrastim (rHuG-CSF) – *Neupogen,*
    - pegfilgrastim – *Neulasta, Neupeg*
  - Lenograstim (G-CSF) – glykosilated
  - Molgramostim (rHuGM-CSF)
  - Sargramostim (rHuGM-CSF) – glycosilated
  - Interleukin 3 (rHu-IL-3) Multi-CSF

- **Indication**
  - Neutropenia
  - Shorten of neutropenic period in cytostatic therapy
  - Prevention of febrile neutropenia

- **Adverse events**
  - Musculoskeletal pain
  - Dysuria
Hemopoietic growth factors (II)

- **Erythropoietin** – glycoprotein – released by peritubular cells in the kidney
  - Epoetin α – *Eprex*, *Epogen*, *Procrit*
  - Epoetin β – *Neorecromon*, *CERA* (PEG-Epo β)
  - Epoetin δ – *Dynepo*
  - Epoetiny: γ, ε, ζ, δ
  - Darbepoetin α - *Aranesp*, *Nespo*
    - **Indication**
      - Anemia Hb below 9-11 g/dl
        » Renal origin
        » CHRI
        » Chemotherapy induced anemia (CIA)
        » In malignant lymphomas, myelomas, MDS
    - **Adverse events**
      - Flu like syndrome
      - Thrombotic vascular complication
      - Increase of BP
Interferones – Immunomodulation cytokines (I)

• **Interferon alpha (IFN α)** – leukocyte – *Roferon (2a), Introna, Viraferon (2b), Infergen (αkon-1)*
  – **Indication** – Oncology, infection diseases

• **Interferon beta (IFN β)** – fibroblastic – *Avonex, Rebif (1a), Betaferon (1b)*
  – **Indication** – Sclerosis multiplex

• **Interferon gamma (IFN γ)** – T-lymphocyte – *Imukin*
  – **Indication** – Infection complications in chronic granulomatosis
Interferons – Imunomodulation cytokines (II)

- **Mode of action of IFN α**
  - Antiproliferative – delays transit from G₁ to S phase
  - Imunomodulation – promote expression of cytotoxic lymphocytes, macrophages and NK-cells participate on induction of cytotoxic reaction
  - Inhibition of viral replication
  - Antitumor activity – suppresses expression of oncogens c-myc, v-myc…

- **Adverse events IFN α**
  - Thrombocytopenia is limiting factor for application of IFN α
  - *Flu-like syndrome* (2 – 4 hr after application, last 4 – 8 hr)
Monoclonal antibodies

- **Murine MAb**
  - 100% murine
  - Hypersensitivity (not in use)

- **Chimeric MAb**
  - 34% murine
  - Hypersensitivity (rituximab)

- **Humanized MAb**
  - 5-10% murine
  - Hypersensitivity (trastuzumab)

- **Human MAb**
  - 100% human
  - Hypersensitivity (panitumumab)
Monoclonal antibodies in oncology

- **Non-conjugated MAb**
  - Direct antitumor activity
    - Induction of apoptosis
    - Interference with receptor and ligand
    - Influence of cytostatics (chemo + MAb – breast cancer)

- **Conjugated MAb**
  - Toxins (pseudomonad, diphteric, ricin)
  - Cytokines
  - Radionuclides
  - Cytostatics
## Monoclonal antibodies in oncology

<table>
<thead>
<tr>
<th>INN</th>
<th>Brand</th>
<th>Target structure</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>trastuzumab</td>
<td>Herceptin</td>
<td>HER-2-neu</td>
<td>Breast Ca</td>
</tr>
<tr>
<td>cetuximab</td>
<td>Erbitux</td>
<td>EGFr</td>
<td>NSCLC, ORL</td>
</tr>
<tr>
<td>bevacizumab</td>
<td>Avastin</td>
<td>VEGF</td>
<td>Various tumors</td>
</tr>
<tr>
<td>rituximab</td>
<td>Mabthera</td>
<td>CD-20</td>
<td>NHL, B-CLL</td>
</tr>
<tr>
<td>ibritumomab</td>
<td>Zevalin</td>
<td>(90Yt) CD-20</td>
<td>NHL</td>
</tr>
<tr>
<td>tositumomab</td>
<td>Bexxar (131I)</td>
<td>(131I) CD-20</td>
<td>NHL</td>
</tr>
<tr>
<td>epratuzumab</td>
<td></td>
<td>CD-22 human.</td>
<td>NHL</td>
</tr>
<tr>
<td>apolizumab</td>
<td></td>
<td>HLA-DR</td>
<td>NHL</td>
</tr>
<tr>
<td>alemtuzumab</td>
<td>MabCampath</td>
<td>CD-52</td>
<td>B-CLL</td>
</tr>
<tr>
<td>gemtuzumab</td>
<td>Mylotarg</td>
<td>CD-33</td>
<td>AML</td>
</tr>
<tr>
<td>oregovomab</td>
<td>Ovarex</td>
<td>CA-125</td>
<td>Ca ovaria</td>
</tr>
<tr>
<td>edrecolomab</td>
<td>Panorex</td>
<td>CO-17-1A</td>
<td>Ca kolorekta</td>
</tr>
<tr>
<td>panitumomab</td>
<td></td>
<td>EGFr</td>
<td>Renal Ca (RCC)</td>
</tr>
</tbody>
</table>
# Inhibition of signal transduction and proteasome

<table>
<thead>
<tr>
<th>INN</th>
<th>Brand</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thyrosinkinase inhibition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>imatinib</td>
<td>Glivec</td>
<td>CML, GIST</td>
</tr>
<tr>
<td>dasatinib</td>
<td>Sprycel</td>
<td>CML</td>
</tr>
<tr>
<td>gefitinib</td>
<td>Iressa</td>
<td>NSCLC, ORL</td>
</tr>
<tr>
<td>erlotinib</td>
<td>Tarceva</td>
<td>NSCLC</td>
</tr>
<tr>
<td>semaxanib</td>
<td>Sugen – withdrawn</td>
<td>Colorectal Ca</td>
</tr>
<tr>
<td>lapatinib</td>
<td>Tykerb</td>
<td>RCC, Breast Ca, H + N</td>
</tr>
<tr>
<td>sorafenib</td>
<td>Nexavar</td>
<td>Liver Ca</td>
</tr>
<tr>
<td><strong>Proteasom inhibition (multikatalytic protease complex)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bortezomib</td>
<td>Velcade</td>
<td>Multiple myeloma, NHL</td>
</tr>
</tbody>
</table>
Targeted antitumor therapy

- Small molecules interfering with intracellular signal transduction
  - EGFR (epidermal)
    - Erlotinib
    - Lapatinib (dual)
    - Gefitinib
  - VEGFR (vascular)
    - Sorafenib
  - PDGFR (thrombocytar)
    - Imatinib
ErbB receptor

- ErbB are tyrosine kinase receptors
- Receptor consist of 4 transmembrane glycoproteins
  ErbB1 - ErbB4
  (HER1 - HER4)
- Structure of ErbB receptor - 3 domains
  - Extracellular (1)
  - Tran membrane (2)
  - Cytoplasmatic with TK activity (3)
  - Similar structure in other TK receptors (VEGFR a PDGFR)
Dimerization of ErbB receptor

- 2 molecules of ErbB receptor conjugates = (homo/hetero forma)
- This active form is capable to transduce external stimuli into the cell
Dimerization of ErbB receptor

ErbB1-1  ErbB2-2  ErbB2-3  ErbB1-2  ErbB2-4
Increased expression of ErbB1 or ErbB2, mutation on ErbB1, and autocrine loop. All are potentially malignant.
Strategy of targeted therapy

- Receptor antagonists
- MAb
- TK inhibitors
- Ligand-toxin conjugates
- Antisense oligonucleotides
Target of action of small molecules

MAb bind to extracellular epitopes may not recognize mutations

Proteolytic cleavage

Small molecules are active in mutations due to different binding site
VEGF receptors in angiogenesis

PIGF, VEGF-A, -B

VEGFR-1 / Flt-1

PI(3,4,5)P3, PI(4,5)P2

PI3-K

PTEN

RAC

PDK1,2

PI3-K

Akt/PKB

FAK

Paxillin

Migration

Angiogenesis

Lymphangiogenesis
Angiogenesis

- Solid tumors above 1-2 mm$^3$ need oxygen and nutrition
- Angiogenesis is the only way
Angiogenesis

- Tumor angioneogenesis is an answer to hypoxia
Angiogenesis

- VEGF are angiogenic factors released by tumor
- VEGF family:
- VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E
Angiogenesis

- VEGFs link to VEGFR receptors of endothelial cell
- 3 VEGF receptors exist: VEGFR-1, VEGFR-2, a VEGFR-3
- VEGFR-1 a VEGFR-2 stimulate angiogenesis, VEGFR-3 stimulates both angiogenesis and lymphangiogenesis
Angiogenesis

- Angiogenesis support tumor and metastatic growth
- Inhibition may influence tumor growth
## Methods to suppress angiogenesis

### Control of angiogenic factors

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>suramin</td>
</tr>
<tr>
<td>antibodies anti VEGF (bevacizumab)</td>
</tr>
<tr>
<td>antibodies anti VEGF receptor</td>
</tr>
<tr>
<td>Proteinkinase inhibitors of VEGF receptor  (sorafenib, semaxanib, pazopanib, SU6668, ZD4190)</td>
</tr>
</tbody>
</table>
Supportive therapy
### Antiemetics in oncology

<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT₃ antagonists setrons</td>
<td>ondansetron, dolasetron, granisetron, tropisetron, palonosetron</td>
</tr>
<tr>
<td>D2/5-HT₃ antagonists substituted benzamides</td>
<td>metoclopramide, alizaprid</td>
</tr>
<tr>
<td>D2 antagonists butyrophenons</td>
<td>haloperidol, droperidol</td>
</tr>
<tr>
<td>D2 antagonists substituted butyrophenons</td>
<td>domperidon</td>
</tr>
<tr>
<td>D2 antagonists fenothiazins</td>
<td>prochlorperazin, chlorpromazin</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>dexamethasone, methylprednisolone</td>
</tr>
<tr>
<td>GABA Benzodiazepins</td>
<td>lorazepam, alprazolam</td>
</tr>
<tr>
<td>Substance P/NK1 antagonists</td>
<td>aprepitant (EMEND)</td>
</tr>
</tbody>
</table>
### League of emetogenic potential

<table>
<thead>
<tr>
<th>&gt;90 %</th>
<th>1. Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Dacarbazin</td>
</tr>
<tr>
<td></td>
<td>3. Dactinomycin</td>
</tr>
<tr>
<td></td>
<td>4. Cyclophosphamid</td>
</tr>
<tr>
<td></td>
<td>5. Carmustin</td>
</tr>
<tr>
<td>60-90 %</td>
<td>6. Prokarbazin</td>
</tr>
<tr>
<td></td>
<td>7. Doxorubicin</td>
</tr>
<tr>
<td></td>
<td>8. Cytarabin</td>
</tr>
<tr>
<td>30-60 %</td>
<td>9. Epirubicin</td>
</tr>
<tr>
<td></td>
<td>10. Ifosfamid</td>
</tr>
<tr>
<td></td>
<td>11. Methotrexat</td>
</tr>
<tr>
<td>10-30 %</td>
<td>12. 5-fluorouracil</td>
</tr>
<tr>
<td></td>
<td>13. Taxans</td>
</tr>
<tr>
<td>&lt;10 %</td>
<td>14. Bleomycin</td>
</tr>
<tr>
<td></td>
<td>15. Vinblastin</td>
</tr>
<tr>
<td></td>
<td>16. Vincristin</td>
</tr>
<tr>
<td></td>
<td>17. Chlorambucil</td>
</tr>
</tbody>
</table>
Emesis in oncology

- **Anticipation**
  - Psychical influence

- **Early**
  - Within first 24 h

- **Delayed**
  - After 24 h
  - Several days
Early and a delayed emesis after platinum therapy
Setrons and emetic reflex

GIT
periphery 5-HT\textsubscript{3} receptors

Afferent n. Vagus

CNS
central 5-HT\textsubscript{3} receptors
Structural formulae of serotonin and some setrons

serotonin

ondansetron

tropisetron

granisetron

dolasetron

hydrodolasetron
Mode of action of setrons

- Activation of 5-HT$_3$ receptor
  - fast depolarization
- Opening of ion channel
  - Transport of Ca$^{++}$ into the cells
- Increased concentration of Ca$^{++}$
  - Neurotransmitter release from n. ending
- Increase of c - GMP
  - Biological answer
Pharmacokinetics of setrons*

<table>
<thead>
<tr>
<th>Drug</th>
<th>$t_{\text{max}}$ (h)</th>
<th>CL (ml/h)</th>
<th>$t_{0,5}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ondansetron</td>
<td>0,8 - 2,0</td>
<td>34 - 36</td>
<td>2,4 - 5,8</td>
</tr>
<tr>
<td>tropisetron</td>
<td>2,0 - 3,0</td>
<td>60**/100</td>
<td>7 - 8**/30 - 40</td>
</tr>
<tr>
<td>granisetron</td>
<td>1,5 - 3,5</td>
<td>15 - 50</td>
<td>3,0 - 10,0</td>
</tr>
<tr>
<td>dolasetron***</td>
<td>0,8 - 1,0</td>
<td>35 - 63</td>
<td>4,0 - 9,0</td>
</tr>
<tr>
<td>palonosetron</td>
<td>-</td>
<td>160t/66r</td>
<td>+/- 40</td>
</tr>
</tbody>
</table>

*) Bioavailability 50 - 80 %, protein binding 65 - 70 %

**) fast metabolization, ***) resp. Hydrodolasetron

$t = \text{total}, r = \text{renal clearance}$
Vomiting centre and connection

- It is not anatomic structure it is function determined part of Area postrema in IV. chamber
- Afferent impulses
  - Not only from GIT, also from peritoneum, gall bladder and liver
  - CNS - intracranial hypertension, psychogenic impulses, vestibule trigger
Area postrema and vomiting center

IV. chamber

Direction of CSF flow

Vomiting center

Nucleus tractus solitarii

Area postrema

CTZ (central trigger zone) is located in Area postrema
Vomiting reflex

- Process of emesis is in general physiological response activated by certain impulses

- Participating
  - Feeling of emesis, gastric stasis, rhythmical contraction of respiratory and abdominal muscles
  - Increased salivation, paleness, sweating

- Vomiting does not replace toxins from organism
Mediators of vomiting reflex

- Serotonin - $5\text{-HT}_3$, antagonists (setrons)
- Dopamine - $D_2$, antagonists (metoclopramide)
- Histamin - $H_1$, antihistamines (difenhidramine)
- Acetylcholine- $M$, anticholinergic (scopolamine)
- Other mediators - e.g. somatostatin, $\gamma$-amino-butyric acid
Classification of 5-HT receptors
### AE of setrons a metoclopramide in %

<table>
<thead>
<tr>
<th></th>
<th>headache</th>
<th>obstipation</th>
<th>diarrhoea</th>
<th>fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>ondansetron</td>
<td>11</td>
<td>4</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>tropisetron</td>
<td>26</td>
<td>14</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>granisetron</td>
<td>18</td>
<td>3</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>dolasetron</td>
<td>22</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>metoclopramide</td>
<td>13</td>
<td>3</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>placebo</td>
<td>6</td>
<td>4</td>
<td>n</td>
<td>4</td>
</tr>
</tbody>
</table>
Substance P/NK1 Antagonists

- **Mode of action**
  - Selective antagonist substance P/NK1 receptors
  - No activity against 5-HT_3, dopaminergic a steroid receptors (= different MoA)
  - Additive effect to above mentioned receptors

- **Pharmacokinetics and interactions**
  - Bioavailability 65%
  - **Metabolism - P-450!!!** (CYP 3A4, CYP 1A2, CYP 2C19)
  - Elimination half live 9 – 13h (55% urine, 45% stool)

- **AE**
  - No significant AEs in comparison with standard therapy setrons and dexamethasone
Outcome of prevention of nausea and vomiting in oncology

- Progress in supportive therapy in oncology
  - Intensifying of highly emetogenic chemotherapy
  - Increase of QoL
  - Improvement of prognosis

Economic consequences?
Economic consequences of the entry of new therapies (example antiemetics)

- Costs of new antiemetics with their economic consequences negligible
  - Higher doses of cytostatics and further intensifying of therapy increase *direct costs*
  - Improvement of prognosis related to further survival, longer and more effective therapy *i.e., increase of direct and indirect costs*