Medical therapies: chemotherapy, endocrine therapy, biological therapies

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Terminology
The biological features of malignancies as targets of tumor inhibitory therapies

- Proliferation, tumor progression (unlimited cell proliferation, erroneous regulation)
- Angiogenesis
- Invasion
- Metastasis
Medical therapies I.

- Modalities
  - Chemotherapy: traditional, empirically developed treatment, interfering with the cells’ survival function
  - Hormone therapy: applied in cancers developed in hormone-responsive organs or tissues, its aim to modulate the effect of the stimulatory hormones
  - Molecular targeted therapies: target molecules that are essential for the survival of special cancers
  - Biological response modifiers: influence complex biological systems
- Systemic vs. local/selective application
- Route of application
  - Intravenous
  - Subcutaneous, intramuscular,
  - Oral,
  - Intraarterial,
  - Interstitial
Medical therapies II.

• According to goal
  – Curative or adjuvant
  – Palliative

• According to schedule
  – Preoperative/neoadjuvant
  – Postoperative/adjuvant
  – Palliative
• Adjuvant therapy: aims at the eradication of microscopic cancer cell colonies, micrometastases left behind, and the prevention of metastases (cure, curative intent)

• Palliative therapy: aims at the reduction of the tumor mass, thus resulting in the amelioration of the symptoms caused by the tumor (the quality of life=QOL, and usually also survival improve)

• Neoadjuvant therapy: aims at the reduction of the locally, regionally advanced tumor („down staging”), operability improves by the „sterilization” of the edges of the tumor, or sometimes metastasectomy may be performed. By eradicating the microscopical tumor particles, an adjuvant effect takes place (curative intent). Neoadjuvant therapy serves as a tool for the estimation of therapy-sensitivity and prognosis. Provides opportunity to modulate therapy according to response
Therapeutic strategy
(based on multidisciplinary consensus)

- Tumor type, histological type, „natural history”
- Stage (clinical and pathological TNM) – local, regional or systemic spread
- Prognostic and predictive factors
- Performance status

Professional guidelines, protocols!
Clinical studies!
Multidisciplinary Team, Tumor board!
Way of action

• Targeting cellular processes
  – Proliferation
  – Angiogenesis inhibition
  – Modulation of immune mechanisms
  – Inhibition of invasion
  – Inhibition of endocrine/paracrine stimulation

• Targeting cellular mechanisms/molecules
  – Chemotherapy (low therapeutic index, many side effects!)
  – Molecular targeted biological therapies
Cell cycle
Traditional antitumor agents: Mechanism of action according to phase specificity

Chemotherapy: Mitosis inhibition

Chemotherapy: DNA-targeted agents

Hormone therapy

Chemotherapy: Antimetabolites, DNA-targeting agents
Chemotherapy
## Cytostatics (chemotherapy agents) according to their target

<table>
<thead>
<tr>
<th>Group</th>
<th>Agent</th>
<th>Target of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolites</td>
<td>5-fluorouracil</td>
<td>Thymidilate synthase</td>
</tr>
<tr>
<td></td>
<td>Metothrexate</td>
<td>Dihydrofolate reductase</td>
</tr>
<tr>
<td></td>
<td>Citosine arabinoside</td>
<td>DNA polymerase</td>
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<td></td>
<td>Gemcitabine</td>
<td>DNA polymerase</td>
</tr>
<tr>
<td>DNA</td>
<td>Cyclophosphamide</td>
<td>Alkylating G, C nucleotides</td>
</tr>
<tr>
<td></td>
<td>Platinum agents</td>
<td>Alkylating G, C nucleotides</td>
</tr>
<tr>
<td>Topoisomerase inhibitors</td>
<td>Irinotecan</td>
<td>Topoisomerase-I</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td>Topoisomerase-II</td>
</tr>
<tr>
<td>Mitotic spindle</td>
<td>Vinca alkaloids</td>
<td>Inhibition of the aggregation of the mitotic tubules</td>
</tr>
<tr>
<td></td>
<td>Taxanes</td>
<td>Inhibition of degradation of the mitotic tubules</td>
</tr>
</tbody>
</table>
### Chemosensitive and chemoresistant malignancies in the adult

<table>
<thead>
<tr>
<th>Chemosensitive</th>
<th>Moderately chemosensitive</th>
<th>Chemoresistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin lymphoma</td>
<td>Breast cancer</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>Agressive non-Hodgkin lymphoma</td>
<td>Non small cell lung cancer</td>
<td>Anaplastic thyroid cancer</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>Ovarian cancer</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Testicular cancer</td>
<td>Colorectal cancer</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td></td>
<td>Gall bladder cancer</td>
</tr>
</tbody>
</table>
Chemotherapy – Way of action

• Phase specificity
• Cycle specificity
Chemotherapy

• Chemosensitivity – chemoresistance
• The importance of dose
• Dosing
• Dose intensity, dose density
• The need of cyclic therapy
• The importance of combinations
  – Polychemotherapy
  – Chemotherapy + molecular targeted agents
• Side effects
Chemoresistance

- Indolent tumor
- Non cell-mediated mechanisms
  - Abnormal vessels
  - Abnormal interstitial pressure
  - Hypoxia, lactate acidosis
  - Absence of lymphatic vessels
- Cell-mediated mechanisms
  - Detoxicating enzymes: GST, Topoisomerase II alfa
  - Abnormal apoptosis regulation
  - Transport mechanisms: MDR P-GP, MDRP

Tumor heterogeneity, clonal selection

MDR P-glykoprotein
The importance of dose intensity and dose density (cyclic chemotherapy)
(Norton L, 1997)

Diagram showing:
- Lower-dose therapy
- Higher-dose therapy
- Dose-dense therapy

Graphs with cell number on the y-axis and time (in weeks) on the x-axis.
The importance of combination chemotherapy (polychemotherapy)

- Different way of action (cycle and phase specificity)
- Different targets (to break drug resistance)
- Different side effects (to lower severity of side effects)
Side effects of chemotherapy

- **Acute** (even after a single therapy)
  - Nausea, vomiting, headache, gastrointestinal symptoms
  - Fever, central nervous symptoms
  - Bone marrow depression (leukopenia, neutropenia, thrombopenia, anaemia)
  - Alopecia, skin and nail abnormalities
  - Renal insufficiency
  - Liver insufficiency

- **Medium-term** (after multiple chemotherapy treatments)
  - Fatigue, amenorrhoea, weight loss, immune deficiency, osteoporosis, neuropathy, „chemo-brain”

- **Late**
  - Low bone marrow reserve function, chronic/definitive heart, kidney, pulmonary function abnormalities, central nervous system sequelae (neuropathy)
Chemotherapy-induced pancytopenia: mucositis
Chemotherapy-induced pancytopenia (thrombopenia): purpura, petechia
Chemotherapy-induced pancytopenia (thrombopenia): petechia
Chemotherapy-induced pancytopenia (thrombopenia): petechia, hematoma
Gemcitabine-induced acute dermatitis

Paclitaxel-induced acute dermatitis

Doxorubicin-induced nail damage
Docetaxel-induced nail damage
Docetaxel-induced pneumonitis
Hormone therapy (Endocrine therapy)
Hormone therapy I.

• Reducing or antagonizing the effects of stimulatory hormones
• Reserved to those cancers that
  – Arise in hormone-dependent tissues, organs (breast, prostate, thyroid etc.), and
  – Do not show ab ovo or acquired hormone resistance
• The effect comes slower than after other treatments (chemo- or radiotherapy)
• It should be maintained long or until relapse/progression
Hormone therapy = blocking hormone production or hormonal effect

- Estrogens
- Progesteron
- Androgens
- PRL
- STH
- IGF-I/insulin
- TSH

A traditional, but still modern „molecular targeted” treatment modality
Hormone therapy II.

• The blockade of hormonal effects may result in
  – the prevention of cancer (chemoprevention)
  – the eradication of the cancer (adjuvant therapy)
  – the regression of the cancer (neoadjuvant and palliative therapy)
Nuclear ER and 17-beta-estradiol: AF1 and AF2 activation
Predictive factors: features of hormone sensitivity, hormone dependence

- (everyday practice: used in breast cancer only)
- High ER/PR expression
- Low proliferative activity (low grade/Ki67, long relapse/progression free period)
- Other biomarkers (IHC): HER2 negativity, bcl-2, pS2 positivity
- Genetic characterisation: „Luminal A”, Oncotype DX, Mammaprint stb, „Sensitivity to Endocrine Therapy” (SET) genomic index (Symmans 2010)
ER IHC 20x magnification

PR IHC 20x magnification

c-erbB-2 IHC 20x magnification
Gene expression profile

ER-positive tumors: Heterogeneous group

Luminal A és B: different prognosis and sensitivity to therapy

Sorlie, 2001
Acquired hormone resistance

• Reversible, adaptative change of the phenotype
• GF-dependent signal transduction dominates
• Its early or late development is a rule
Estrogen suppressive and antagonist therapies

- LHRH analogs
- Gonadotropines (FSH + LH)
- ACTH
- Adrenal glands
- Pituitary
- Ovaries
- LHRH (hypothalamus)
- oophorectomy
- Androgens
- Estrogens
- Aromatase inhibitor
- Fulvestrant
- SERM

ACTH, adrenocorticotrope-hormone
FSH, folliculus-stimulatory hormone
LH, luteinizing hormone
LHRH, LH-releasing hormone
Peripheric conversion (aromatisation)
Estrogen suppressive and antagonist therapies II.

- Ovarian ablation: premenopause
- SERM (tamoxifen, toremifene): estradiol competitive inhibition
- Pure antiestrogen (fulvestrant): ER destabilisator
- Aromatase inhibitors: reduce estrogen synthesis
- Gestagens: direct tumor effect and pituitary suppression
Andrew V. Schally, Nobel laureate in 1977 for the discovery and synthesis of hypothalamic releasing hormones, for the hormone analog theory and the development of several peptide hormone analogs.
LHRH agonists: mode of action II.

LH hypersecretion, an acute effect

LH hyposcretion, during continuous administration
LHRH analogs: mode of action I.

LHRH (hypothalamus) → Pituitary → Gonadotrop hormones (FSH + LH) → Ovaries → Estrogens

Progesterone → Breast

Down-regulation of the LHRH receptors
Hormonal effects of LHRH analogs

Side effects of ovarian suppression therapies

- Hot flashes, sweating
- Irritable mood, vegetative disorders
- Change of skin and hair
- Sexual changes
- Weight gain
- Arthralgia
- Osteoporosis
Nuclear ER and SERMs: AF1 activation, slow ER degradation
Antiestrogens: SERMs

Estradiol

Fulvestrant (‘Faslodex’)

Tamoxifen

Raloxifene
The side effects of SERM therapy

- Hot flashes
- Weights gain
- Thrombosis, thromboembolism
- Endometrium stimulation
- Stroke
- Cataract
Aromatase inhibitors: Blockade of estrogen synthesis

**Cholesterol**
- 20,22-Lyase
  - Pregnenolone

**Pregnenolone**
- 17α-Hydroxylase
  - 17α-Hydroxypregnenolone

**17α-Hydroxypregnenolone**
- (intermediate)
  - 11β-Hydroxylase
    - 11-Deoxycortisol
  - 21α-Hydroxylase
    - 11-Deoxycorticosterone

**11-Deoxycorticosterone**
- 18-Hydroxylase
  - Aldosterone

**Progesterone**
- 17α-Hydroxylase
  - 17α-Hydroxyprogesterone

**17α-Hydroxyprogesterone**
- (intermediate)
  - 17,20-Lyase
    - Androstenedione

**Androstenedione**
- aromatase
  - Testosterone

**Testosterone**
- Oestrone

**Oestrone**
- Pharmacological Target
  - Oestradiol
In situ estrogen synthesis (breast cancer)
Circulating and *in situ* estrogen concentrations
Aromatase inhibition

Type I inhibitor (= steroidal) (target's substrate-binding site)

Androgen

Oestrogen

Cytochrome P450

Aromatase molecule

NADP⁺

NADPH

Type II inhibitor (= non-steroidal) (target's cytochrome P450 'aromatase')
Aromatase inhibitors

- Steroidal inhibitors (type I inhibitors)
  - 1st generation
    - Formestane (4-Hydroxyandrostendione)
  - 2nd generation
    - Exemestane (FCE 24304)
  - 3rd generation
    - Atamestane

- Non-steroidal inhibitors (type II inhibitors)
  - 1st generation
    - Aminoglutethimide
  - 2nd generation
    - Fadrozole (CGS 16949A)
  - 3rd generation
    - Letrozole (CGS 20267)
    - Anastrozole (JCI D 1033)
    - Vorazole (R-83842)
Side effects of aromatase inhibitor therapy

• Arthralgia, myalgia
• Osteoporosis
• Fatigue, hot flushes, nausea, diarrhoea
• Deepening of estrogen deficiency: alopecia, sexual changes
Fulvestrant (Faslodex):
AF1 and AF2 inhibition in the nucleus, ER degradation
# Hormone therapy in breast cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>Mode of action</th>
<th>Agent</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHRH analogs/oophorectomy</td>
<td>Abrogation of ovarian hormone production</td>
<td>Goserelin, Triptorelin</td>
<td>Premenopause</td>
</tr>
<tr>
<td>SERM (selective ER modulator)</td>
<td>ER-antagonis, ER competitive inhibition</td>
<td>Tamoxifen, raloxifene</td>
<td>Premenopause and postmenopause</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>Extragonadal estrogen synthesis inhibition</td>
<td>Anastrozole, letrozole, exemestane</td>
<td>Postmenopause</td>
</tr>
<tr>
<td>Pure antiestrogen</td>
<td>ER destruction</td>
<td>Fulvestrant</td>
<td>Postmenopause</td>
</tr>
<tr>
<td>Gestagens</td>
<td>Direct tumor inhibition and hypophysis suppression</td>
<td>Megesztrol acetate, medroxyprogesteron acetate</td>
<td>Postmenopause</td>
</tr>
</tbody>
</table>
Imaging complete response after 1 year of letrozole
Core-biopsy: invasive ductal cancer grade 1
Surgical specimen: pathologic complete regression, TRG-4
Metastatic breast cancer: Case 1

- 39-yr old, 6 years ago quadrantectomy + ABD.
- H: IDC Grade III, pT1(12 mm), pN0(0/10), ER:80%, PR:90% positive, HER2 IH+FISH: negátiw
- Postoperative RT
- Multiple pulmonary metastases and enlarged mediastinal lymph nodes, 7 cycles of Taxotere-Epirubicin chemotherapy, complete regression; febrile neutropenia, thrombosis, amenorrhea.
- 2 months after the chemotherapy, symptomless (imaging) progression (estradiol, FSH, LH in the premenopausal range)
Metastatic breast cancer: Case 1

Zoladex+Femara therapy, CR, maintained for > 8 years (in the last years without Zoladex)
Metastatic breast cancer: Case 2

- 72-yr old, 7 years ago mastectomy and ABD
- H: mixed cancer, pT2, pN1(3/4)
- Postoperative RT, 4 cycles of CMF chemotherapy, and tamoxifen 4 years
- Routine US detected the thrombosis of the left jugular vein due to the metastases of the upper mediastinal lymph nodes, but no other distant metastases
Metastatic breast cancer: Case 2

- Letrozole therapy: complete regression lasting 14 months
Androgen suppressive and antagonist therapies

- **Enzyme inhibition**: Finasteride; Duasteride
  - 5-alpha-reductase
  - Testosterone → Dihydrotestosterone

- **Hormone synthesis inhibition**: Flutamide; Bicalutamide

- **Receptor inhibition**: LHRH agonists, antagonists or estrogen

- **Hormone synthesis inhibition**: Ketoconazole

- **Hypothalamus**: LHRH
- **Pituitary**: LH → Testis
- **Testis**: LH → Testosterone
- **Tumor**: Flutamide; Bicalutamide
- **Adrenal**: Ketoconazole

**Note:** This diagram illustrates the mechanisms of action for androgen suppression and antagonism, including enzyme inhibition, receptor inhibition, and hormone synthesis inhibition.
# Hormone therapy in prostate cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>Mode of action</th>
<th>Agents</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHRH analogs/orchiectomy</td>
<td>Abrogation of testicular hormone production</td>
<td>Goserelin, Triptorelin</td>
<td>Impotence, osteoporosis,</td>
</tr>
<tr>
<td>Antiandrogens</td>
<td>Kompetetive antagonist of testosterone</td>
<td>Flutamid, biculatamid, nilutamid</td>
<td>Hot flushes, diarrhoea, gynecomastia, osteoporosis, hepatotoxicity</td>
</tr>
<tr>
<td>Androgen synthesis inhibitor</td>
<td>Extragonadal testosterone synthesis inhibition</td>
<td>Ketokonazol</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>5-alfa reductase inhibitor</td>
<td>Inhibition of testosterone activation (DHT)</td>
<td>Finasteride</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Total androgen blockade (TAB)</td>
<td>Inhibition of all androgens</td>
<td>LHRH analog + antiandrogen</td>
<td>Impotence, osteoporosis</td>
</tr>
</tbody>
</table>
Insulin/IGF-I reduction

- Diabetes type 2 metabolic disorder (hyperglycemia, insulin resistance):
  - insulin, IGF-I IGF-II↑
  - IGFBP ↓
  - SHBG↓
  - sex hormones↑
  - inflammation (ROS, cytokines, adipokines)↑
Insulin/IGF-I reduction

• Metformin effect (AMPK-mediated dose and time-dependent effect):
  – Endocrine effects: glukoneogenesis↓, blood sugar, insulin, IGF-I, IGF-II↓
  – Direct cell effects: mTOR inhibition (proliferation/apoptosis), cyclin D, HIF1alpha, MYC inhibition, functional p53 reexpression

• Results: proliferation, angiogenesis, inflammation↓
Molecular targeted/biological therapies
Molecular targets of tumor inhibitory therapies

- Acts as a condition of malignant phenotype
- Biological role/importance
- Possible to detect or measure in the cancer or other biological sample
- Related to outcome
- Its inhibition results in the regression of the cancer
Features of traditional and molecular targeted therapies

<table>
<thead>
<tr>
<th>Introduction</th>
<th>Place of action</th>
<th>Efficient dose</th>
<th>Dose escalation</th>
<th>Side effects</th>
<th>Potentiates conventional therapies</th>
<th>Resistance evolves</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Empirical</td>
<td>Efficient</td>
<td>Efficient</td>
<td>Frequent, rapid</td>
<td>No</td>
<td>Delayed</td>
</tr>
<tr>
<td></td>
<td>Non selective</td>
<td>&gt; Maximal</td>
<td>Efficient</td>
<td></td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td>tolerated</td>
<td>Important</td>
<td></td>
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<tr>
<td></td>
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<td>dose</td>
<td>Important</td>
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<td></td>
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<td>&lt;</td>
<td>Important</td>
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<thead>
<tr>
<th>Konvencionális terápiák (chemotherapy and radiotherapy)</th>
<th>Molecular targeted therapies</th>
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</thead>
<tbody>
<tr>
<td>Developed on scientific basis</td>
<td>Non selective</td>
</tr>
<tr>
<td>Selective</td>
<td>&gt; Maximal tolerated dose</td>
</tr>
<tr>
<td>&lt; maximal tolerated dose</td>
<td>Efficient</td>
</tr>
<tr>
<td>Instead optimal combination</td>
<td>Important</td>
</tr>
<tr>
<td>Not important</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>Frequent, rapid</td>
</tr>
<tr>
<td>Delayed</td>
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</table>
Targets of molecular targeted therapies

• In the cancer cell
• In the microenvironment of the cancer
Inhibition of the Growth Factor signal transduction system

- HER2-inhibition: trastuzumab (Herceptin®, Roche)
- EGFR (HER1) inhibition: gefitinib (ZD-1839, Iressa®, AstraZeneca), erlotinib (OSI-774, Tarceva®, Roche)
- Dual HER1/HER2 tírosine kinase inhibition: lapatinib (GW-572016, Tyceerb®, GSK)
- mTOR inhibition: everolimus (RAD 001)
The HER2 anomaly

Overexpression of the HER2 (human epidermal growth factor-2) receptor

HER2 negative cell

HER2 positive cell
Methods for the detection of HER2 amplification/overexpression

DNA: gene amplification
- FISH
- PCR
- Southern blot

mRNA
- Northern blot

Protein
- IHC
- Western blot

Extracellular domain
- ELISA

FISH

CISH
Trastuzumab (Herceptin®, Roche): The first molecular targeted agent in the treatment of breast cancer and solid tumors

Recombinant humanized IgG1 monoclonal antibody against HER2

Inhibition of cancer cells through HER2 blockade, and antibody-mediated cytotoxicity
Targets of molecular targeted therapies

• In the cancer cell
• In the microenvironment of the cancer
The biological basis of angiogenesis inhibition in cancer therapy

• Tumor progression depends on blood supply

• Angiogenesis induced by the tumor results in pathological blood vessels which act against the efficiency of chemotherapy and radiotherapy

• High vessel density is a poor prognostic factor

• Angiogenesis precedes malignant transformation
Activation of Vascular Endothelial Cells

- Tumor cells
- Host cells
- PDGF
- VEGF
- PDGF receptor
- VEGF receptor
- FGF
- FGF receptor
- Signal transduction cascade
- Mitotic spindle
- Proliferation
- Invasion
- Migration
- Degradation of basement membrane
- Permeability
- Capillary tube formation
Endothelial Cell Proliferation, Migration, and Differentiation

- Tumor cells
- Extracellular matrix
- MMPs
- Integrins
- FGF
- VEGF
- PDGF
- Mitotic spindle
- Vessel lumen
Stabilization/Maturation of New Blood Vessels

- Tumor cells
- PDGF
- Ang-1
- VEGF
- FGF
- Endothelial cell
- Pericyte
- Blood vessel
VEGFR-2 Pathway and Function

Endothelial Cell

Growth, Migration, Permeability, Anti-apoptosis
The inhibition of angiogenesis normalizes tumor vasculature

Decreeses interstitial pressure and increased vessel density

Increases drug intratumoral concentration

**Molecular targeted agents according their mode of action**

<table>
<thead>
<tr>
<th>GROWTH FACTORS</th>
<th>VEGF inhibition:</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGF, PDGF, VEGF, IGF…</td>
<td>bevacizumab</td>
</tr>
</tbody>
</table>

**SIGNAL TRANSDUCTION SYSTEM**
- Farnesyl transferase inhibitors
  - Tipifarnib
  - Lonafarnib
- RAF inhibitors
  - Sorafenib
- BCR/ABL inhibitors
  - Imatinib, nilotinib

**GROWTH FACTOR RECEPTORS**
- Tyrosine kinase inhibitors:
  - **EGFR**: erlotinib
gefitinib, trastuzumab,
lapatinib, cetuximab,
- **PDGFR**: sorafenib,
imatinib
- **VEGFR**: sorafenib, sunitinib
- mTOR inhibitors: temsirolimus,
everolimus
Possible reasons of resistance to molecular targeted agents

• The target is not functional, i.e. not a condition of cancer cell survival
• Altered function of the target
• Mutation
• Other signal transduction routes dominate
• Increased destruction of the agent
Other biological agents targeting complex biological systems

• Interferon-alfa
• Interleukin-2
Typical acneiform dermatitis during anti-EGF receptor therapy
Typical acneiform dermatitis during anti-EGF receptor therapy
Typical nail changes (paronychia) during anti-EGF receptor therapy
• 54-year old breast cancer patient with HER2 positive advanced breast cancer
• Treatment with Taxotere-Carboplatin, and Herceptin results in complete remission
- 31-year old patient with HER2 positive advanced breast cancer
- Treatment with Taxol plus Herceptin yields complete remission
Young HER2 negative breast cancer patients with multiple organ metastases
Therapy: bevacizumab-paclitaxel
Complete tumor regression after 4 months of treatment
Drug development in oncology

• ADME tests
  – Absorption, distribution, metabolism, elimination

• Clinical studies
  – Phase I
  – Phase II
  – Phase III
  – Phase IV
Key factors to increase efficiency

• Optimal patient selection, individual therapy based on prognostic and predictive factors

• New agents