Hormonal Therapy
Targeted Therapy
Tumor Markers

Dr. Martin Matějů
Hormonal Therapy

• 18th century – observation: no prostatic cancer among eunuchs
• 1896 Beatson was the first to perform OE on patient with BC => regression of chest wall mts
• The oldest targeted therapy
• Used mainly for cancers derived from hormonally responsive tissue
Hormonal Therapy

= manipulation of the endocrine system by:

a) Exogenous administration of specific hormones

b) Administration of drugs which inhibit the production or activity of hormones

c) Surgical removal of endocrine organs (OE, AE)
## Hormonal Therapy - List

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# GnRH Analogs

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GnRH Analogs

GnRH = Gonadotropin releasing hormon
• Stimulates releasing of LH and FSH
• Induce a CHEMICAL CASTRATION
• Week of ↑↑ synthesis of LH and FSH leads to down-regulation of LH and FSH receptor in either ovaries or testes and to ↓↓ of sex hormones down to castration (menopausal) levels
• (!concetrations of FSH and LH are increased!)
• Initially the levels of sex hormones are increased before they decrease (need of hormone antagonist – TOTAL BLOCKADE)

_Goserelein_ – prostate cancer, breast cancer, …
# Aromatase Inhibitors

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Aromatase Inhibitors

- Used in postmenopausal women with ER positive BC
- AR is a member of cytochrome P450 superfamily – convert androgens produced by adrenal glands fatty tissue to estrogens
- AI competitively and reversibly inhibit AR
- *Letrozol, Anastrozol – Breast Cancer*
### SERM’s

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SERM´s (Selective Estrogen Receptor Modulator)

ANTAGONISTS ON ESTROGEN RECEPTOR

*Tamoxifen*
- Partial agonist on ER – depends on tissue (e.g. Endometrium)
- Used in both early and advanced pre and postmenopausal women
- Tamoxifen itself is a prodrug which needs metabolic activation in liver by the cytochrome P450 – several isoforms - some do not really activate (bad metabolisers) => TMX is not working in these patients

*Fulvestrant*
- estrogen receptor antagonist with no agonist effects
- works both by down-regulating and by degrading the ER
- in postmenopausal women with disease progression following TMX therapy
# Antiandrogens

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Antiandrogens

• Antagonists of androgen receptors
• Often used together with GnRH or surgical castration – **Total blockade**
• Treatment of prostate cancer

*Flutamide, Bicalutamide*

• competes with testosterone and its powerful metabolite, dihydrotestosterone (DHT), for binding to androgen receptors in the prostate gland
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specific hormone agonists may have a growth-inhibiting, or even cytotoxic effect on tumor cells

**Progestagens (megestrol) – BC**

**Androgeny (fluoxymesteron) - BC**

**Estrogeny (diethylstilbestrol) - Prostate Cancer**

**Corticosteroids (prednison) – CLL, mm, lymphomas**

- ↓ incorporation of uridin to RNA => ↓ efficiency of RNA polymerase => ↓ of RNA and protein synthesis
**Somatostatin Analogs**

*Octreotid, Sandostatin*

- Analog of the peptide hormone somatostatin
- Inhibits the production of numerous peptide hormones of the gastrointestinal system, including *insulin*, *glucagon*, *pancreatic polypeptide*, *gastric inhibitory polypeptide*, and *gastrin*
- Used for suppression of the hormonal syndromes which accompany several pancreatic islet cell tumors, including the Zollinger-Ellison syndrome of *gastrinoma* and the chronic hypoglycemia of *insulinoma*. It is also effective in suppression of the *carcinoid* syndrome or chronic diarrhea of *VIPoma syndrome*. 
Targeted Therapy
Targeted Therapy

• Type of medication that blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth

• Therefore maybe less harmful to normal cells
## Targeted Therapy - List

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Targeted Therapy - Schema

**Hematologic malignancies**
- Rituximab (Rituxan)
- $^{90}$Y-Ibritumomab tiuxetan (Zevalin)
- $^{131}$I-Tositumomab (Bexxar)
- Gemtuzumab ozogamicin (Mylotarg)
- Alemtuzumab (Campath)

**Solid tumors**
- Lapatinib (Tykerb)
- Erlotinib (Tarceva)
- Gefitinib (Iressa)
- Sorafenib (Nexavar)
- Sunitinib (Sutent)
- Trastuzumab (Herceptin)
- Cetuximab (Erbitux)
- Panitumumab (Vectibix)
- Bevacizumab (Avastin)

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## Monoclonal Antibodies Against RTKs

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**Monoclonal antibodies ("-mab")**
- Cetuximab, Transtuzumab
- Bevacizumab
- Rituximab, Alemtuzumab, Gemtuzumab
- Erlotinib, Lapatinib, Gefitinib
- Imatinib, Bosutinib, Lestaurtinib

**Tyrosine kinase inhibitors ("-nib") (small molecules)**
- Erlotinib, Lapatinib, Gefitinib
- Imatinib, Bosutinib, Lestaurtinib
Receptor Tyrosine Kinase

- Transmembrane proteins with an intracellular kinase domain and an extracellular domain that binds ligand
- RTKs need to form dimers that are stabilized by ligand
- Interaction between the two cytoplasmic domains stimulates autophosphorylation of tyrosines causing their conformational changes and activate the kinase domain by initiating signaling cascades of phosphorylation of downstream cytoplasmic molecules
- These signals are essential to various cellular processes, such as control of cell growth, differentiation, metabolism, and migration.
Monoclonal Antibodies Against RTKs

Cetuximab (Erbitux)
- chimeric (mouse/human) monoclonal antibody, against epidermal growth factor receptor (EGFR)
- Indicated for (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer (mCRC)

Panitumab (Vectibix)
- human monoclonal antibody, against EGFR

Trastuzumab (Herceptin)
- Human monoclonal antibody, against Human epidermal growth factor receptor 2 (Erb2=HER2/neu; )
- Indicated for HER2 overexpressed BC
- in CZ the overexpression must be confirmed by immunohistochemistry as well as FISH (confirms the amplification of Her2/neu gene)
- Cardiotoxic
### Other Monoclonal Antibodies Used in Solid Tumors

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Other Monoclonal Antibodies Used in Solid Tumors

Bevacizumab (Avastin)

- Humanized monoclonal antibody that recognizes and blocks vascular endothelial growth factor (VEGF) from creating new blood vessels
- First clinically available angiogenesis inhibitor
- With standard chemotherapy for metastatic colon cancer
- Clinical studies are underway in other even non-metastatic cancers
### Monoclonal Antibodies Used in Leukemia/Lymphoma

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Monoclonal Antibodies Used in Leukemia/Lymphoma

Rituximab (MabThera)
- chimeric monoclonal antibody against the protein CD20 found on mature B cells
- treatment of lymphomas, leukemias, and some autoimmune disorders

Alemtuzumab
- targets CD52 protein present on the surface of mature lymphocytes but not on the stem cells from which these lymphocytes are derived
- second-line therapy for B-CLL

Gemtuzumab
- monoclonal antibody to CD33 expressed in most leukemic blast cells
- used to treat acute myelogenous leukemia
# Tyrosine Kinase Inhibitors Connected to RTKs

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Protein kinase inhibitors

• Type of enzyme inhibitors that specifically blocks the action of one or more protein kinases
• They can be characterised by the amino acids whose phosphorylation is inhibited
• Most kinases act on both serine and threonine
• The tyrosine kinases act on tyrosine
• Dual-specificity kinases act on all three
iRTKs targeting Erb (epidermal growth factor receptor) family TKs:

• **HER1/EGFR:**
  - Erlotinib
  - Binds in a reversible fashion to the ATP binding site of the receptor
  - By inhibiting ATP binding, the autophosphorylation is not possible and the signal is stopped
  - Used in advanced NSCLC after failing at least one line of CHT

Gefitinib
- Similar to Erlotinib
- NSCLC

Lapatinib
- inhibits receptor signal processes by binding to the ATP-binding pocket of the EGFR/HER2 protein kinase domain, preventing self-phosphorylation and subsequent activation of the signal mechanism
- Used in HER2/neu overexpressed Breast cancer

Neratinib
- HER2/neu:
  - Lapatinib
  - Neratinib
iRTKs targeting RTK class III:

Sunitinib (Sutent)
- multi-targeted RTK inhibitor (PDGF-Rs, VEGFRs, KIT (CD117), RET …)
- Used in RCC and imatinib resistant GIST

Sorafenib (Nexavar)
- small molecular inhibitor of several Tyrosine protein kinases
- is unique in targeting the MAP Kinase pathway
- Used in advanced RCC and HCC
iRTKs targeting VEGFR (vascular endothelial growth factor) TKs:

Vandetanib
Semaxanib
Cediranib
Axitinib
Sunitinib
Sorafenib
Toceranib
Regorafenib
# Non – Receptor Tyrosine Kinase Inhibitors

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Non – Receptor Tyrosine Kinase Inhibitors

Imatinib
- Used in GIST and CML
- In CML, the Philadelphia chromosome (t(9;22)) leads to a fusion protein of \textit{abl} with \textit{bcr} (breakpoint cluster region), termed \textit{bcr-abl}. As this is now a continuously active tyrosine kinase, imatinib is used to decrease \textit{bcr-abl} activity
- is quite selective for \textit{bcr-abl} – it does also inhibit other targets c-kit and PDGF-R

Bosutinib – Src kinase
Other

Aflibercept - fusion protein against VEGF

Denileukin diftitox
- exotoxin against IL-2
- Used in Leukemia and Lymphoma
TUMOR MARKERS
Tumor Markers

• Substance found in the blood, urine or body tissues that can be elevated in cancer
• They are used in oncology to help detect the presence of cancer
• An elevated level of a tumor marker can indicate cancer; however, there can also be other causes of the elevation
• None used either for screening of healthy population nor for diagnostic of asymptomatic patients
Tumor Markers can be produced:

1. directly by tumor cells
2. by non-tumor cells as a response to the presence of a tumor

Ideal Tumor Marker characteristics:

1. Corresponds with certain type of malignity (↑ specificity)
2. Easy detection (method)
3. Early detection of disease and relapse (↑ sensitivity)
4. Corresponds with stage/extend of disease
5. Corresponds with a course of therapy and prognosis
Tumor Marker Trajectory

PSA values in relapsing prostate cancer

- Normal levels
- Prostate cancer dg.
- Hormonal Therapy
- Remission
- Relapsing disease
- Chemotherapy
Cancer-specific markers

- Related to the presence of certain cancerous tissue
- Not specific in making a diagnosis
- But useful to describe progress of the disease or response to the treatment
- E.g. higher level of CEA in patient with history of bowel cancer can be indicative for extensive examining (CT/PET, endoscopy…)
- CEA (GIT Ca); CA19-9 (pankreatic Ca); CA125 (Ovarian Ca);
Tissue-specific markers

- Related to specific tissues which might have developed cancer
- Not specifically related to the tumor, and may be present at elevated levels when no cancer is present
- Elevated levels point to a specific tissue being suspicious of developing a cancer
- E.g. ↑ PSA level in men – examining prostate tissue; ↑ HCG and AFP – search for testicular or liver cancer respectively
Biochemical Classification of TM

1. Humoral TM
   - Oncofetal Antigens (CEA, AFP, PSA, CA 15-3, ...)
   - Enzymes (NSE, TK, LD, ...)
   - Hormones (hCG, PRL, PTH, ADH, ...)
   - Plasmatic proteins (Ferritin, β2M, Paraproteins, ...)
   - Others (HIAA, VMK ...)

2. Cellular TM (ER, PR, HER2/neu ...)

3. Genetic TM (ATM, APC, BRCA1/2, p53, Rb1 ...)

Humoral TM
- Oncofetal Antigens

**CEA** (Carcinoembryonic antigen)
- normally produced during fetal development in epithelial cells
- ↑ ca GIT, Breast Ca, Lung Ca

**AFP** (α-fetoprotein)
- major plasma protein produced by the yolk sac and the liver during fetal life („fetal albumin“)
- AFP levels decrease gradually after birth
- ↑ nonseminomatous germ cell tumors (testicular cancer, ovarian cancer, and malignant teratoma) and in hepatocellular carcinoma
PSA (Prostate-specific antigen)
- Elevated in the presence of prostate cancer and in other prostate disorders
- Serine protease enzyme
- Reference ranges for prostate-specific antigen increase with age (<2.5 ug/l < 50y; <5 ug/l < 60y; 8.5 < ug/l > 60y)
- Most PSA in the blood is bound to serum proteins. A small amount is not protein bound and is called free PSA.
- The risk of cancer increases if the free to total ratio (fPSA/tPSA) is less than 25%.
Humoral TM
- Oncofetal Antigens

CA = carbohydrate Ag + no. of monoclonal Ig

CA 15-3: ↑ Breast Ca

CA 19-9: ↑ Pancreatic Ca, Gastric Ca, CRC

CA 72-4: ↑ Gastric, Esophageal, Lung and OC

CA 125: ↑ OC
Humoral TM
- Oncofetal Antigens

TPA (Tissue Polypeptid Ag)
- Proliferative Ag
- Fragments of cytokeratins (20)
- Plasmatic level is proportional to mts. Growth

CYFRA 21-1
- Fragments of cytokeratin 19 – Lung Ca
Humoral TM
- Enzymes

Clinical significance
- Nonspecific increase of enzymatic activity of certain organs
- Overproduction of enzymes typically expressed in fetal tissue

LD - testicular tu, leukemia, Renal Ca
ALP - ↑ sarcomas
ACP - skeletal mts of prostate cancer
GMT - ↑ liver mts
NSE - (neuron specific enolase) ↑ neuroblastoma, retinoblastoma, melanoma, SCLC
TK - (thymidin kinase) ↑ leukemia, lymphoms
Humoral TM - Hormones

hCG – (Human Chorionic Gonadotropin)
  ↑chorioCa, germinal testes or ovarial tu

PRL – ↑ prolactinom

Kalcitonin – ↑ medullary ca of Thyroid gland

Thyreoglobulin ↑ folicullar ca of Thyroid gland
Humoral TM - Plasmatic proteins

Ferritin – ↑ multiple myeloma, AML, HD

β2M – ↑ multiple myeloma, CLL, Lymphomas

Paraproteins – ↑ light Ig chains – multiple myeloma
Humoral TM - Others
VMA (Vanil mandelin acid) – ↑ adrenal gland tumor
HIAA (5- hydoxy Indol Acetic Acid) - ↑ urine of patients with neuroendocrine tumor

Cellular TM
ER, PR, HER2/neu ...

Genetic TM
ATM, APC, BRCA1/2, p53, Rb1 ...