Treatment of Breast Cancer

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Breast Cancer - Epidemiology

- Hungary: 7500 cases/year, mortality: 2300/year
- Incidence is increasing with age
- Male breast cancer: ~1%

More than 1 million cases are diagnosed worldwide in every year

Every 7th women is affected !!!
Screening

- Target group: **45-65 years** old women
- X-Ray Mammography - in every 2 year

- 5-7% of the screened patients are called back
  - In 1-2%: malignant tumor is confirmed
  - Dominantly DCIS

- **Goal: detection in an early stage!**

  Participation rate: **only 40-45 %** of the target population

  **70% attendance could decrease mortality with 30% !!!**
Tumor growth and detectability

METASTATIC POTENTIAL: FROM THE EARLIEST POINT!
Staging - TNM

- **Stage 0**: Tis
- **Stage I**: T1/N0,1mi
- **Stage II**: T1-3/N0-1
- **Stage IIIA**: T1-3/N1-2
- **Stage IIIB/C**: T4/N0-2
- **Stage IV**: AnyT/N3

M1
# Early vs. Metastatic Breast Cancer

<table>
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<th>Metastatic</th>
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| **5-ys survival rate:**  
  • With therapy > 80% | **5-ys survival rate:**  
  • With therapy: ~ 15% |
| **Therapeutic Goals:**  
  • Eradicate the tumor  
  • Eradicate the micrometastases  
  • Prevent the recurrence  
  • CURATIVE intentions | **Therapeutic Goals:**  
  • Increase the progression free period  
  • Increase the overall survival  
  • Treat the symptoms (**palliation**)  
  • Quality of life! |

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**Different!**
DECISION MAKING IN THE TUMOR BOARD

- Diagnostic imaging
- Pathology
- Molecular pathology

Biological behavior of the tumor

- Performance status
- Co-morbidities
- Patients’ preference

- Evidence based medicine
- Guidelines

- Cost/benefit
- Financing issues

Dank, 2007
Surgery

- Treat the primary
- Remove axillary lymph nodes
- Metastasectomies

Systemic treatment

- systemic control
  - PST-NAC
  - Adjuvant
  - Palliative

Irradiation

- locoregional control
  - adjuvant
  - palliative

Sentinel vs. ABD

Targeting

Detection

Removal

Radical Mastectomy

Modified Radical Mastectomy

Breast conserving surgery
Aims of the systemic treatment

- Neoadjuvant therapy
  - Down-staging, organ conserving surgery
  - *In vivo* test of chemosensitivity
- Adjuvant therapy
  - Eradicate the micrometastases
  - Increasing OS, RFS, PFS
- Palliative treatment
  - In case of life threatening conditions
  - Increasing the quality of life
Systemic therapy

• Chemotherapy
  – „standard” treatment

• Hormone therapy
  – First targeted therapeutic option!
  – Long lasting therapy for hormone sensitive tumors

• Targeted therapies
  – Individualized, personalized therapy
  – Biomarker based – extensive use of the tools of molecular pathology
Chemotherapy I.
Chemotherapy II.
**Cytotoxic agents**

- **Advantages**: directly affects cell proliferation, targets the dividing cells
- **Disadvantages**: not selective for tumor cells

- During the chemotherapy we are applying the **maximal dose which could be tolerated** by the individual
- However, the **therapeutic index*** is quite low
  - adverse events and side effects are quite common, mostly in the continuously renewable cells of the human body – i.e. bone marrow, GI system, hair follicles

- Continuous treatment could cause lethal bone marrow deficiencies – therefore intermittent, **cyclical** therapy is applied, in every 2-3 weeks, to give the sufficient time for regeneration

*Therapeutic index = toxic dose (LD50) / therapeutic dose (ED50)
Targets of the cytotoxic treatments

DNA synthesis

**Antimetabolites**
- Similar structures to normal metabolites, BUT able to block the metabolical pathways as false metabolites
- i.e.: - Antifolates (MTX)
  - Pirimidin antagonists (SFU)
  - Dezoxicitidin analogues (GEM)

**Covalent** binding to the nucleophil parts of the DNA, to the guanin, citozin or adenin nucleotids

**Intercalation**
- i.e.: Topoisomerase inhibitors
- i.e.: Anthracyclines (ADM, EpiADM)

**Transcription**

**DNA synthesis**

**Duplication**

**Interception**

**Mitosis**

**Alkylating agents**
- i.e.: cyclophosphamide

**Komplexing antibiotics**
- i.e.: bleomycin
- i.e.: actinomycin

**Platina vegyületek**
- i.e.: - cisplatin
- i.e.: - carboplatin

**Mitotic spindle inhibitors**
- i.e.: Taxanes (TXT, TAX)

- intercalation to the DNA,
- stabilization of the DNA-topoisomerase complex
- inhibition of the topoisomerase functions
  → the DNA therefore fragmented

Prevents the formation of the mitotic spindle by inhibiting microtubules, therefore stops the proliferation in the G2-M phase of the cycle.
Cytostatic agents – inhibiting cell proliferation and signaling pathways

- **Targets:** molecular mechanisms which are maintaining the malignant signalization
- **Do not cause direct cell damage**
- But they are preventing the signaling pathways which cause the malignant growth
- Molecular targets are well defined: preventing tumor growth by
  - blocking cell proliferation
  - Or an indirect manner by modifying the environtment of the tumors

- Administration: due to the reversible binding between the drug and target molecule the maintenance of the drug levels in the blood is crucial – but cumulating toxicity could cause several side effects!

- **Side effects are different than that in case of cytotoxic agents**
- Most frequent ones are like skin rashes, diarrhea and immune-suppression

Hormonotherapy  | Monoclonal antibody therapy  | Tyrosin kinase inhibitors
More than 1000 targeted therapeutic options, at least 4 mechanism of action

Receptor binding and inhibition - mAbs

Angiogenesis inhibition

Immunotherapies, vaccines

Signal transduction inhibitors - TKIs
Biomarkers are necessary

- prediction
- monitoring
- prognostics

BUT! Tumor **heterogeneity**
- **Intratumoral differences**
- **Primary** and **metastatic** tumors could behave very differently
## Tumor characteristics

- Positive axillary lymph nodes
- Tumor size
- Lymphovascular invasion
- Histological tumor type
- Histological grade

## Biological markers

- ER/PR
- HER2 overexpression
- Ki-67 LI, mitotic index
Predictive and prognostic markers

• **Predicting the therapeutic response:**
  – Hormone receptor expression (ER, PR)
  – Her2
  – Proliferation markers ie. Ki-67 LI

• **Clinical Outcome:**
  – TNM, axillary involvement
  – Histological tumor type
  – Grade, differentiation
  – Her2 expression
  – mutant p53
  – Proliferation markers ie. Ki-67 LI
  – claudin, E-cadherin, CK 5/6
Molecular subtype

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Sandhu et al., Microarray-Based Gene Expression Profiling For Molecular Classification of Breast Cancer and Identification of New Targets for Therapy
Hormone therapy: continuously evolving in the last 50 years

- Antiestrogens
- Aromatase inhibitors
- GnRH analogues

- Easy to apply:
  - daily per os or
  - injection in every month or every 3 months

- New drugs with lower toxicity

source: Lecture of Rajib Bhattacharjee: Hormonal therapy of breast cancer
http://www.slideshare.net/rajibbhattacharjee5/hormone-therapy-in-breast-cancer/6,
Anti-estrogenes

- **Steroids**: fulvestrant
  - Clear anti-estrogen, palliative setting
- **Non steroids**: tamoxifen
  - Most successful anti-estrogen
  - Selective Estrogen Receptor Modulator (SERM).
  
  - **SERMs** (tamoxifen) have both *antiestrogen and estrogen-like effects* depending on the organs/tissues

  ✓ Tamoxifen has **anti-estrogen** effects in the breast

  ✓ In the bones, endometrium, and liver it has **estrogen-like** effects – therefore did not cause osteoporosis, but it could cause endometrium hyperplasia!

  ✓ It has got a **favorable** effect on the lipid profile and decreases the incidence of cardiovascular diseases, however, the **risk** of thromboembolic events is higher.
Aromatase inhibitors

• Mechanism of action: inhibiting the estrogen synthesis
  – **Tissue** level: ovary granulosa cells, fat tissue in postmenopausal patients
  + blocks the local synthesis in the **tumor**

• **Type I.**: *exemestan*
  – Steroid-like aromatase inhibitors
  – irreversible binding to the substrate binding part of the enzyme
  – specific and long lasting binding

• **Type II**: letrozol, *anastrozol*
  – Non-steroid aromatase inhibitors
  – reversible binding to the cytochrome P450 part of the aromatase enzyme complex

• Aromatase inhibitors are successfully applied **adjuvantly** (proved to be as effective as tamoxifen) and in the **metastatic** setting (whereas they proved to be more effective than tamoxifen – i.e. ATAC Trial)
GnRH agonists

- goserelin
- leuprolelin

- **GnRH (LHRH)-agonists** – with ovarium inhibition they are successfully inhibiting tumor progression
- ER-positive cancers: as effective as surgical removal of the ovaries - BUT reversible!
- Applied together with tamoxifen: maximal estrogen depletion → significantly increased tumor response and disease-free survival in case of premenopausal, hormone positive tumors
Hormone therapy – what to do in case of a progression?

• BUT! Hormone sensitive could decrease! Based on the possible mechanism of hormone resistance **new targets** are under investigation
  – the mutations of the estrogen receptor
  – alternative, estrogen independent activation cascades (i.e PI3K/Akt/mTOR and RAS-RAF-MAPK signaling pathways)
1970
• **CMF** (Bonadonna)
  • cyclophosphamid, methotrexat, fluorouracil

1980
• **Antracyclines**
  • doxorubicin, epirubicin

1990
• **Taxanes**
  • paclitaxel, docetaxel

2005
• **Anti- HER-2 therapy**
25% of the breast tumors are HER-2 positive
Pathological diagnostics

Overexpression (protein)

Gene amplification (DNS)

IHC

FISH
From clinical trials to daily practice


EBC, early breast cancer
MBC, metastatic breast cancer
MGC, metastatic gastric cancer
Targeted therapies against the Her2

1. **Metastatic** breast cancer – until progression or unacceptable toxicities (Slamon et al., Gasparini et al., Marty et al.)
   
   *Survival increased dramatically: PFS increased with more than 6 months*

2. Treatment of **early** breast cancer (FinHER, HERA, NSABP B31): Adjuvant trastuzumab therapy given for 1 year

   *increases both PFS and OS and reduces the risk of relapse with more than 50%*

3. **Neoadjuvant** trastuzumab (NOAH, GeparQuattro)

   *pCR rate was nearly duplicated compared to chemotherapy alone!*

Dank M, Tőkes T, 2013
New trastuzumab indication: neoadjuvant therapy

New form of administration: subcutaneous trastuzumab

New mechanism of action: pertuzumab

New entity and mechanism of action: T-DM1

Anti-Her2 antibody therapy
Pertuzumab – first Her2-Her3 dimerization inhibitor

**EMA : 2013. March 13.!

**HER2/HER3 dimerization

- HER2/HER3 dimerization inhibition: pertuzumab
- trastuzumab + pertuzumab

DUAL INHIBITION

Ahn ER, 2012
Pertuzumab – a new game-changer in Her2-positive metastatic BC


Progression free survival (month)

Before 1998 | 1998- 2013 | 2013-

4,6\(^1\) | 11 – 12,4\(^2,3,4\) | 18,5\(^4\)

PFS increased with another 6 months

Chemo therapy

Trastuzumab + Chemo therapy

Pertuzumab + Trastuzumab + Chemo therapy
Pertuzumab – first Her2-Her3 dimerization inhibitor

- **Metastatic** or locally advanced disease

- **Together** with trastuzumab and chemotherapy: dual inhibition, more effective combinational therapy

- Dramatically **increases** OS and DFS

- Cardiac toxicity: **equivalent** to trastuzumab
Antibody-drug conjugate: trastuzumab-emtansine (T-DM1)

- ADC: antibody-drug conjugate
  - Targeted agent – mAb
  - „linker”
  - Citotoxic agent

- Targeted chemotherapy, carried by a targeted agent directly to the tumor cell – less side-effects

- Trastuzumab prevents tumor growth, and decreases metastatic potential, meanwhile the emtansin binds to the tubulin and prevents DNA replication

mAb, monoclonal antibody.

PFS was significantly improved with T-DM1 compared with physician's choice: Median PFS 6.2 months [95% CI 5.59–6.87] vs 3.3 months [2.89–4.14]; ([HR] 0.528 [0.422–0.661]; p<0.0001).

Intravenous vs. subcutaneous injection

Average administration times:

90,5/42,9 min.

vs.

3,3 min.!

Trastuzumab SC optimizes therapy and decreases the costs of the treatment
TNBC: lack of „targets”

TNBC: „ER–, PgR–, HER2–” breast cancer

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Angiogenesis

Small tumor (1-2 mm)
• Avascular
• Occult

Bigger tumor
• Vascularization
• Metastatic potential

Angiogenic "switch"

Mediator: VEGF
Stages of tumor development in which angiogenesis is a crucial factor

VEGF: a predominant proangiogenetic factor from the earliest point of tumor development

Poon et al, 2001
Bevacizumab

- A successful VEGF inhibitor

- In case of BC applied as 1st line therapy in combination with paclitaxel – OS increased in Her2 negative breast cancer!
  - E2100-study (BEV+paclitaxel): Median PFS increased with **5,6 months**
  - AVF3694g-study (BEV+capecitabine): Median PFS increased with **2,9 months**

- Hungary: applied based on European Guidelines and EMA
- Preventing the resorption of the bone, by reducing osteoclast activity
- Enhancing anti-tumor immune activity
- Inducing the apoptosis in the tumor cells
- Preventing tumor cell migration and metastatases formation

Bone metastases? ↓

Bisphosphonates!
- zolendronate
- ibandronate
- pamidronate
Combinational treatment

- Different mechanisms of action
- Different resistancy mechanisms

- Toxicities and side effects

Quality of Life!!!!
Side effects
Chemotherapy

Mucositis
Nausea/vomiting
Diarrhea
Cystitis
Sterility
Myalgia
Neuropathy
Alopecia
Pulmonary fibrosis
Cardiotoxicity
Local reaction
Renal failure
Myelosuppression
Phlebitis
Side effects

Cardiac toxicity: CT vs. Trastuzumab

**Type I.**
(pl. doxorubicin)

- cellular destruction
- Biopsy: structural changes
- Cumulative/dose related
- IRREVERSIBLE damage

**Type II.**
(pl. trastuzumab)

- cellular disfunction
- Biopsy: lack of structural changes
- Not cumulative and not related to the dose
- REVERSIBLE

Ewer & Ewer 2008
Side effects

Hormone Therapies

• Menopausa-like symptoms
• Joint pain, rheumatoid-symptoms
• Tamoxifen – endometrium hyperplasia!!!

Bevacizumab

• Hypertonia!
• Fatigue, diarrhea
• thrombosis, wound healing problems, epistaxis
• GI perforations, fistules
• proteinuria
Supportation

- Cytoprotection
- Antiemetic drug
- Analgetics
- Skin protection

- Goal: Increase the QUALITY OF LIFE
- Managing, treating and preventing the side effects - both tumor and therapy-related symptoms
Metastatic disease

• **Aims of the treatment:**
  – To treat and reduce the symptoms
  – Increase the OS
  – Reduce the tumor burden, delay the progression

• Highly **depending** on
  – The earlier therapeutical lines
  – Biological behavior
  – Co-morbidities

• **Patients’ preference**
  – Compliance, adherence to the therapies
  – Side effects which have an effect on their daily routine

**QUALITY OF LIFE!!!**
Thank you for your attention

Don’t worry, I had the same thing, and they cured me!