Cellular, Molecular, and Biochemical Targets in Breast Cancer

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“One size fits all” surgical treatment of breast cancer

Wilhelm Fabricus Hidanus
1660-1634
Mastectomy

Halstead’s Radical Mastectomy

Johns Hopkins Hospital Reports, 4:297, 1894–1895
Developments in Surgical Management of Breast Cancer

- 1890s-1970s: Radical mastectomy
- 1970s: (B-04) Radical mastectomy = Total mastectomy (+/- XRT, delayed axillary management)
- 1980s: (B-06) Total mastectomy = Lumpectomy + XRT
- 1980-1990s: Sentinel lymphadenectomy
- 2000s: (ACOSOC Z001) Narrowed indications for axillary lymphadenectomy
Heterogeneity of Breast Cancer

• Stage (size, nodal status)
• Focal versus multicentric
• Histology (type, grade proliferative rate)
• Hormonal status
• Her 2 overexpression
• Molecular profile
Systemic Treatment based on tumor characteristics

- **Hormone-receptor Positive (60%-70%)**
  - Anti-hormonal Therapy

- **HER2 Positive (20%-25%)**
  - Anti-HER2 Therapy

- **Triple-Negative (~15%)**
  - Chemo
Systemic Treatment based on tumor characteristics

Hormone-receptor Positive (60%-70%)

Anti-hormonal Therapy

- Tamoxifen
  - Selective estrogen receptor modulator
  - Pre- or post-menopausal
- Aromatase inhibitors
  - Block conversion to estrogen
  - Do not completely suppress ovarian function
  - Post menopausal
Systemic Treatment based on tumor characteristics

- **Human Epidermal growth factor Receptor 2**
- Her2 is amplified in 25-30% of breast cancers
- Trastuzumab (herceptin) = antibody against extracellular domain
- Pertuzumab = antibody against extracellular domain
- Lapatinib = antibody against intracellular domain

**HER2 Positive (20%-25%)**

**Anti-HER2 Therapy**
Systemic Treatment based on tumor characteristics

- **AC** = doxorubicin (anthracycline) + cyclophosphamide
- **TC** = docetaxel (taxane) + cyclophosphamide
- **TAC** = docetaxel + doxorubicin + cyclophosphamide

- **Trastuzumab based therapies**
  - **AC** + herceptin
  - **TCH** = docetaxel, carboplatin, herceptin

**Triple-Negative (~15%)**
Patient Information

Age: 60
Comorbidity: Minor Problems
ER Status: Undefined
Tumor Grade: Undefined
Tumor Size: 2.1 - 3.0 cm
Positive Nodes: 1 - 3
Calculate For: Mortality
10 Year Risk: 42 Prognostic

Adjuvant Therapy Effectiveness

horn: Overview 98 (Tamoxifen)
chem: Overview 98 (CMF-Like)

Hormonal Therapy: 20
Chemotherapy: 10
Combined Therapy: 28

No additional therapy:
- 52.8 alive in 10 years.
- 40.4 die due to cancer.
- 6.8 die of other causes.

With hormonal therapy: Benefit = 6.2 alive.

With chemotherapy: Benefit = 3.0 alive.

With combined therapy: Benefit = 8.8 alive.

www.adjuvantonline.com
Oncotype Dx

- Microarray used to describe tumor’s genetic phenotype
- 21 gene analysis
  => recurrence score
  => response to chemotherapy

Breast Cancer: Targets on the Horizon

• Vascular Endothelial Growth Factor inhibitors
• PolyADP Ribose Polymerase inhibitors
• PI3 Kinase inhibitors
• mTOR antagonists
• Histone Deacetylation inhibitors
• IGFR inhibitors
• Notch inhibitors
• Src inhibitors
VEGF Inhibition (Bevacizumab)

- Humanized monoclonal antibody
- Binds to and neutralizes VEGF
- Inhibits angiogenesis
- In combination with chemotherapy, improves progression free survival in metastatic triple negative breast cancer (+3 months)
- No clear evidence supporting use in neoadjuvant setting


Bear et al. The effect on pCR of bevacizumab and/or antimetabolites added to standard neoadjuvant chemotherapy; NSABP protocol B-40. *Journal of Clinical Oncology* 2011; 29:81s.
PARP Inhibition (olaparib, iniparib, veliparib)

- Poly-A-Ribose Polymerase repairs DNA single strand breaks
  - Target tumor deficiencies in DNA repair?
  - Synergize with DNA damaging therapeutics (chemo, XRT)?
- Positive results in Phase II trial of iniparib in combination with chemotherapy for metastatic triple negative breast cancer (improved response rate, progression free survival, and overall survival)
- No difference (in progression free or overall survival) in Phase III trial

PI3K/akt/mTOR Pathway Inhibition

- Important in tumor proliferation, metabolism, invasion, angiogenesis, cell survival
- Overactivation in some triple-negative breast cancers

References

• Bear et al. The effect on pCR of bevacizumab and/or antimetabolites added to standard neoadjuvant chemotherapy; NSABP protocol B-40. *Journal of Clinical Oncology* 2011; 29:81s.
• O’Shaughnessy et al. Meta-analysis of patients with triple-negative breast cancer from three randomized trials of first-line bevacizumab and chemotherapy treatment for metastatic breast cancer. *Cancer Research* 2010; 70:452s.
Thank you

• Ingrid Meszoely
• Vanderbilt Breast Center
Surveillance/Treatment is Guided by Risk Profile

- GAIL Model
- Clauss Model