Systemic Therapy for Metastatic Breast Cancer: Goals and Drug Categories

Julie R. Gralow, M.D.
Director, Breast Medical Oncology
Jill Bennett Endowed Professor of Breast Cancer
Professor, Global Health
University of Washington School of Medicine
Fred Hutchinson Cancer Research Center
Seattle Cancer Care Alliance
Treatment of Metastatic Breast Cancer: Goals

- Metastatic breast cancer is not curable, but is treatable
- Goals:
  - Control and regression of disease
  - Prolongation of life
  - Improvement in symptoms and quality of life
Trends in Metastatic Breast Cancer Treatment

- Treatment increasingly dependent on gene/protein expression
- Metastatic cancer patients living longer with better quality of life
Metastatic Breast Cancer Survival in USA: Impact of New Agents

Endocrine therapy + Chemotherapy + Targeted therapy

**FIGURE 1.** Overall survival from time of recurrence.

Giordano S et al, Cancer 100:44-52, 2004
European School of Oncology (ESO)  
Advanced Breast Cancer Guidelines  
Initial Workup

- Minimal staging workup for metastatic breast cancer includes:
  - History and physical examination
  - Hematology and biochemistry tests
  - Imaging of chest, abdomen and bone

- Biopsy of a metastatic lesion should be performed, if easily accessible, to confirm metastatic diagnosis
  - Biologic markers (ER, HER2) should be reassessed at least once in the metastatic setting, if clinically feasible
Restaging

- Determining effectiveness of therapy:
  - Evaluation of response to therapy should occur every 2-4 months for endocrine therapy, every 2-4 cycles for chemotherapy
  - Depends on dynamics of disease, location and extent of metastatic involvement, type of treatment
Choices in the Treatment of Metastatic Breast Cancer

- Choice of treatment is based on many factors:
  - Patient age, menopausal status, general health and functional status
  - Tumor ER status, HER-2 status
  - Previous treatments
  - Extent and sites of disease
  - Available therapies in the patient’s country
Endocrine Therapy in Breast Cancer

Aromatase inhibitors, ovarian suppression

Estrogen

Estrogen Receptor

SERMS, SERDS

Cell Growth and Division
Endocrine Therapy for Metastatic Breast Cancer

- Endocrine therapy is the preferred choice for ER+ metastatic breast cancer
  - Less side effects than chemotherapy

- Exceptions:
  - Concern or proof of endocrine resistance
  - Need for fast response (location, symptoms)

Antineoplastic drugs relevant to breast cancer

- **Endocrine therapy:**
  - Tamoxifen
  - Anastrozole (Arimidex)
  - Leuprolide (Lupron)

Strategies for Overcoming Resistance to Endocrine Therapy:

Many proteins, genes and pathways play a role in breast cancer

- mTOR inhibitors (everolimus)
- CDK4/6 Inhibitors (palbociclib)
- PI3 Kinase Inhibitors
- AKT Inhibitors
- HDAC Inhibitors
Optimizing HER-2 Targeted Therapy: 4 FDA-Approved Drugs with HER2 as a Target

- Pertuzumab: Anti-HER-2 Antibody
- Trastuzumab: Anti-HER-2 Antibody
- Lapatinib: Dual HER-1/HER-2 Tyrosine Kinase Inhibitor
- Ado-trastuzumab emtansine: Antibody-Drug Conjugate

Diagram: HER-2 receptors on cancer cell, nucleus, and cell division pathways.
Chemotherapy +/- Trastuzumab in Metastatic Breast Cancer: Overall Survival


65 % of Chemo-alone group crossed over to trastuzumab at progression
Antineoplastic drugs relevant to breast cancer

- Targeted Therapy
  - Trastuzumab (Herceptin)
European School of Oncology Guideline: HER2 Targeted Therapy for Metastatic Breast Cancer

- Anti-HER2 therapy should be offered early to all HER2+ metastatic breast cancer patients unless contraindicated (or unavailable)
- Optimal duration of anti-HER2 therapy for metastatic breast cancer (when to stop) unknown
Chemotherapy for Metastatic Breast Cancer

- Optimal agents
- Treatment schedules
- Monotherapy vs. combination regimens
- Maintaining quality of life, minimizing toxicity
WHO Model List of Essential Medicines

Antineoplastic drugs relevant to breast cancer

- **Chemotherapy:**
  - Doxorubicin (Adriamycin)
  - Cyclophosphamide (Cytoxan)
  - Paclitaxel (Taxol)
  - Docetaxel (Taxotere)
  - Fluorouracil (5-FU)
  - Methotrexate

- **Chemotherapy (cont):**
  - Carboplatin
  - Gemcitabine (Gemzar)
  - Capecitabine (Xeloda)
  - Vinorelbine (Navelbine)

• Sequential single agent chemotherapy is generally the preferred choice
  – Less toxicity than combination chemo
  – No data to support optimal sequence
• Combination chemotherapy is reserved for patients with:
  – Rapid clinical progression
  – Life-threatening visceral metastases
  – Need for rapid symptom/disease control
• Chosen regimen should be evidence-based, with proven efficacy and acceptable toxicity
Chemotherapy is the primary systemic therapy option for triple negative breast cancer

6 subtypes of TNBC identified by gene expression array

**Basal-like 1 and 2 (BL1, BL2)**
- High expression of cell cycle and DNA response genes
- More responsive to **platinum** chemotherapy

**Immunomodulatory (IM)**

**Mesenchymal (M) and Mesenchymal-Stem Like (MSL)**
- Enriched for genes associated with epithelial-mesenchymal transition
- Responsive to **mTOR, PI3K, abl-src pathway** drugs

**Luminal Androgen Receptor (LAR)**
- Sensitive to **androgen receptor** drugs (enzalutamide, bicalutamide)
Targeting the Cancer Environment: Bone Inhibition

cancer cells

Growth Factors

osteoblasts, macrophages

osteoclasts

Growth Factors
• Bone modifying agents should be routinely used in combination with other systemic therapy in patients with bone metastases
  – Bisphosphonates (pamidronate, zoledronic acid)
  – RANK ligand inhibitor (denosumab)
• Agents should be started early, if possible before onset of bone symptoms
  – These agents reduce fractures, the need for radiation or surgery, and other complications
• Should be continued even in presence of disease progression
Systemic Therapy for Metastatic Breast Cancer: A Balancing Act

Balancing treatment efficacy and toxicity is a major objective

Quantity of Life

Quality of Life