Management of HER2+ Metastatic Breast Cancer

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Overview

• Brief History of HER2+ MBC
  – The landscape has changed!

• Receptor Discordance
  – What does this mean? How do we manage this?

• Overview of therapies to treat HER2+ MBC
History of HER2 – 30 years in the making

The *neu* oncogene: an *erb-B*-related gene encoding a 185,000- Mr tumour antigen

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A series of rat neuro/glioblastomas all contain the same transforming gene (*neu*) which induces synthesis of a tumour antigen of relative molecular mass (Mr) 185,000 (p185). The *neu* oncogene bears homology to *erb-B* and the tumour antigen, p185, is serologically related to the epidermal growth factor (EGF) receptor. The two proteins, EGF receptor and p185 appear to be distinct, as they coexist in nontransformed Rat-1 cells.

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Beyond Breast Cancer
Development of Targeted Therapy

The New England Journal of Medicine

Overall Survival Benefit With Lapatinib in Combination With Trastuzumab for Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer: Final Results From the EGF104000 Study

Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer
What is receptor discordance?

- **Def’n of Discordance (per Websters):**
  - The state of not agreeing, being out of harmony or being in variance
- **Which receptors?**
  - ER, PR and HER2
- **Other terms:** “Receptor Shift,” “Tumor heterogeneity”
Incidence of Receptor Discordance

In the literature, discordance rates between primaries and metastases are:

- ER: 13% - 16%
- PR: 39% - 41%
- Her2: 12 – 17%

*Important to re-biopsy metastatic sites for both diagnosis and receptor status!*

Dieci et al. Annals of Oncology 2009
Tumor Heterogeneity and Clones within individual tumors
Real world management

- 45 year old female
- 2007: Stage II ER/PR+/Her2+ breast cancer
- AC → TH → Herceptin X 1 year, Tamoxifen
- 2010: recurrence in bone and liver on Tam
- Bx ER+/PR-/Her2-
- 2010 – 2013: Letrozole → faslodex → aromasin/everolimus → Capecitabine → weekly taxol
- 2013: re-Biopsy: ER/PR weak+/Her2+
- Taxol/trastuzumab/pertuzumab
- 2014: TDM1 to current
Moving on to management of HER2+ MBC

• What is in our toolkit?
  – Trastuzumab
  – Pertuzumab
  – TDM1
  – Lapatinib
  – Combinations of all of the above
HER2+ MBC Roadmap
A little science and a lot of new drugs....

[Diagram showing pathways for Trastuzumab, Pertuzumab, Lapatinib, T-DM1, RN2, and other molecules involving HER2 and HER3 with interactions at the cellular level involving RTK, RAS, PI3K, MEK, AKT, and mTOR pathways.]
Trastuzumab in the treatment HER2+ BC improves survival

.....Where we were in 2001
First Line Therapy for HER2+ MBC: Pertuzumab (Cleopatra) ....Where we are in 2014

Randomized 1:1, 2-Arm, Open-Label, Multicenter Trial

- First-line HER2+ MBC or recurrent locally advanced patients (N = 808)
- Trastuzumab + docetaxel + pertuzumab
- Trastuzumab + docetaxel + placebo

Primary Efficacy Endpoint: PFS

Baselga et al. NEJM 2012
Key lessons learned from Cleopatra…

• #1: Women who received pertuzumab with trastuzumab/taxane faired better than those who received placebo
  – On average, 6 additional months free from progression
  – At 3 years of follow-up, improved SURVIVAL!

• #2 Toxicities were manageable between groups
  – No difference in cardiac toxicity
  – Clinically, more diarrhea w/ pertuzumab

Baselga et al. NEJM 2012
Second Line Therapy for HER2+ MBC: TDM1 (Emilia)

“Trojan horse” approach
Second Line Therapy for HER2+ MBC: TDM1 (Emilia)

Patients with HER2+ MBC following treatment with a taxane and trastuzumab (N = 980)

- T-DM1 3.6 mg/kg IV q3w (n = 490)
- Capecitabine 1000 mg/m² PO BID, Days 1-14, q3w
  Lapatinib 1250 mg/day PO (n = 490)

Verma et al. NEJM 2012
What did we learn from Emilia?

• #1: Women who received TDM1 fared better than those who received Cape/Lapatinib
  – On average, 3 additional months free from progression
  – Again, improved SURVIVAL!

• #2 Toxicities differed between groups
  – Lapatinib/Cape = Diarrhea, rash
  – TDM1 = low blood counts, elevated liver enzymes
    • With both regimens, hair loss is minimal
Which is better in the first line? Pertuzumab or TDM1

1st-Line HER2+ MBC
MARIANNE Phase III Study

Centrally HER2+ recurrent locally advanced
-or-
Untreated MBC

n=1092

Trastuzumab + Taxane

T-DM1 + Pertuzumab

T-DM1 + Placebo

Rx until progressive disease
Third Line and Beyond: Lapatinib combinations

Patients with HER2+ (FISH/IHC3+) MBC and progression on anthracycline, taxane, and trastuzumab

- Lapatinib 1500 mg/day PO (n = 148)
- Lapatinib 1000 mg/day PO + Trastuzumab 4 mg/kg → 2 mg/kg IV wkly (n = 148)

Note: No traditional chemotherapy given, only HER2-targeted therapy

Blackwell et al. JCO 2010
Should we combine Her2-directed agents?

YES

• #1 Addition of trastuzumab to lapatinib resulted in improved SURVIVAL for women in this study

• #2 From a side effect profile, might be a nice alternative to chemotherapy plus trastuzumab
  - Watch closely for diarrhea
A few HER2-targeting drugs to keep your eye on

• Neratinib (oral, similar to lapatinib)
  – Irreversible binding to HER1 and HER2

• Afatinib
  – Also inhibits HER1 and HER2

• MM-302
  – HER2-targeting liposomal doxorubicin
Conclusions

• Significant progress in treatment of HER2+ MBC

• New drugs, new sequences, new combinations

• Goal is continued improvement in survival and quality of life
Thanks!

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