Managing Breast Cancer Brain Metastases
Carey K. Anders, MD
November 2014
Brief Overview

• Challenges faced
• Subtype predilection and prognosis
• Local therapy  
  – Focused radiation  
  – Radiosensitizers
• Systemic approaches  
  – Chemotherapy and targeted agents  
  – Novel clinical trials  
  – Preclinical Studies
Breast cancer Brain Metastases: Challenges faced…

• Devastating, feared and increasingly common consequence of breast cancer
  – Incidence 30% Her2+\(^1\), 50% triple negative\(^2\) advanced BC
• Blood brain barrier, efflux pumps in brain endothelium limit exposure to cytotoxics
• Until recently, preclinical model systems were scarce
• Clinical trials frequently exclude patients with CNS disease
  – Trials specifically targeting patients with brain metastases few

\(^1\) Bendell et al. Cancer 2003
\(^2\) Lin et al. Cancer 2008
The Blood Brain Barrier

The blood–brain barrier (BBB)

Expert Reviews in Molecular Medicine ©2003 Cambridge University Press
How well do we understand the BBB?

Estimate of BBB Penetration of Common Cytotoxics

Cytotoxics with CNS activity (Case reports/small series)

- CMF
- CAF
- Cisplatin
- Carboplatin
- Capecitabine
- Temozolomide
- Irinotecan
- Methotrexate

*Km = the unidirectional transfer coefficient → BBB permeability

Muldoon et al. JCO, 2007
Is the BBB intact in breast cancer brain metastases?

231-BR-Her2 Brain metastases

$^{14}$C-paclitaxel

$^{14}$C-paclitaxel AUC ($\mu$g.hr/g)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>AUC (µg.hr/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>0.18</td>
</tr>
<tr>
<td>Avg brain metastasis</td>
<td>2.9</td>
</tr>
<tr>
<td>Peripheral tissues</td>
<td>80-400</td>
</tr>
</tbody>
</table>

Lockman et al. Clin Cancer Res 2010
Subtype-Specific Patterns of Metastases

Luminal B
Luminal A
Her2
Normal
Basal-like

Smid et al. CCR 2008
Brain Metastases Signature preferentially expressed in Basal-like and Claudin-low tumors

<table>
<thead>
<tr>
<th>Intrinsic Subtype</th>
<th>All (Metastases Free Survival)</th>
<th>Brain (Metastases Free Survival)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P value</td>
</tr>
<tr>
<td>LumB v. LumA</td>
<td>1.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Basal v. LumA</td>
<td>2.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HER2 vs. LumA</td>
<td>2.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Claudin-low vs. LumA</td>
<td>1.5</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Harrell et al. BCRT 2012
Subtype Specific Differences in Prognosis

<table>
<thead>
<tr>
<th></th>
<th>Median survival (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients (222 patients)</td>
</tr>
<tr>
<td>Disease-free survival (years)</td>
<td>1.7 (0–31)</td>
</tr>
<tr>
<td>Overall survival (years)</td>
<td>4.1 (0.1–32)</td>
</tr>
<tr>
<td>Survival from detection of brain metastases (months)</td>
<td>8 (0.2–56)</td>
</tr>
</tbody>
</table>
Prognostic Differences by Receipt of Systemic Therapy

<table>
<thead>
<tr>
<th>Biological subtype</th>
<th>No systemic Chth/Ht</th>
<th>Chth/Ht</th>
<th>Chth/Ht with trastuzumab</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple negative</td>
<td>3</td>
<td>4</td>
<td>–</td>
<td>0.21</td>
</tr>
<tr>
<td>HER2(positive) ER/PgR(−)</td>
<td>4</td>
<td>8</td>
<td>10</td>
<td>0.004</td>
</tr>
<tr>
<td>HER2(positive) ER/PgR(+)</td>
<td>2</td>
<td>8</td>
<td>13</td>
<td>0.0000</td>
</tr>
<tr>
<td>Luminal</td>
<td>3</td>
<td>14</td>
<td>–</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Differences in Clinical Behavior of Brain Metastases by Subtype

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>HER2+</th>
<th>TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from Met Dx to CNS Relapse</td>
<td>~1 yr</td>
<td>&lt;6 months</td>
</tr>
<tr>
<td>Control of extracranial dz at time of CNS relapse</td>
<td>~50%</td>
<td>uncommon</td>
</tr>
<tr>
<td>Median OS from time of CNS relapse</td>
<td>Up to 1-2 yr</td>
<td>3-5 months</td>
</tr>
<tr>
<td>Impact of systemic therapy after WBRT</td>
<td>Longer OS (retrospective)</td>
<td>?</td>
</tr>
<tr>
<td>Cause of death</td>
<td>Up to 50% due to CNS PD</td>
<td>Rarely due to CNS PD alone</td>
</tr>
</tbody>
</table>
# Overview of Local Therapy for Breast Cancer Brain Metastases

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Reference</th>
<th>Sample Size</th>
<th>No. Brain Lesions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT +/- surgery</td>
<td>Patchell et al. NEJM 1990</td>
<td>n = 48 (10% breast)</td>
<td>Single</td>
<td>OS 40 vs. 15 wks (p &lt; 0.01)</td>
</tr>
<tr>
<td>WBRT +/- SRS (RTOG 9508)</td>
<td>Andrews et al. Lancet 2004</td>
<td>n=333, (10% breast)</td>
<td>1 - 3</td>
<td>OS 6.5 vs. 4.9 mos. w/ single met (p=0.04)</td>
</tr>
<tr>
<td>SRS +/- WBRT</td>
<td>Aoyama et al. JAMA 2006</td>
<td>n = 132 (10% breast)</td>
<td>1 - 4</td>
<td>OS 8 v. 7.5 mos, (p = 0.4)</td>
</tr>
<tr>
<td>SRS +/- WBRT</td>
<td>Chang et al. Lancet 2009</td>
<td>n = 58* (15% breast )</td>
<td>1 - 3</td>
<td>2X (52% vs 24%) &gt; risk 4 mos NC decline w/ WBRT ; OS favored SRS alone</td>
</tr>
</tbody>
</table>

*Trial stopped early; accrual goal n = 90.
What do we tell our patients…
SRS vs. WBRT vs. Both??

• In **select** patient populations:
  – Improved OS adding SRS to WBRT in 1 lesion
  – No difference in OS by adding WBRT to SRS if < 4 lesions
  – Neuro-cognitive decline worse if WBRT added to SRS, but higher rates of intracranial progression.

**Take-home point:** Discuss fear of intracranial recurrence versus neuro-cognitive decline with patients to determine whether or not to include WBRT upfront who are candidates for SRS….
Update on radiosensitizers plus WBRT

- Meta-analysis of RCT’s to compare WBRT +/- radiosensitizers found no improvement in OS\(^1\)
  - Multiple tumor types, various NC and QOL scales

<table>
<thead>
<tr>
<th>Agent &amp; MOA</th>
<th>Study Design</th>
<th>Reference</th>
<th>N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motexafin gadolinium:</td>
<td>WBRT +/- Motexafin</td>
<td>Mehta et al. 2003</td>
<td>401 (30% breast)</td>
<td>No diff OS (4.9 vs. 5.2 mos, NS)</td>
</tr>
<tr>
<td>Generates reactive O2 species in cancer cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efaproxiral:</td>
<td>WBRT +/- Efaproxiral</td>
<td>Suh et al. 2008</td>
<td>368 (100% breast)</td>
<td>No diff in OS (7.5 vs. 8.5, NS)</td>
</tr>
<tr>
<td>Increases oxygenation in hypoxic tumor cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trasutuzumab: moAb targeting HER2</td>
<td>WBRT + trastuzumab</td>
<td>Chargari et al. 2010</td>
<td>31 (100% breast)</td>
<td>6 wk RR 74.2% (19% CR); TTP (CNS) 10.5 mo</td>
</tr>
</tbody>
</table>

*Other agents: TMZ (Ph II, mixed results), lapatinib + capecitabine (CR in case report, Abboud 2010).

\(^1\)Viani et al. J of Exp Clin Canc Res 2009
## Current Trials evaluating radiosensitizers plus WBRT

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Institution</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT +/- Capecitabine</td>
<td>Phase II</td>
<td>Baylor Hoffman-La Roche</td>
<td>N = 25 N = 130</td>
</tr>
<tr>
<td>Lapatinib + WBRT</td>
<td>Phase II</td>
<td>Hellenic Cooperative Oncology Group</td>
<td>N = 81 (lung/breast)</td>
</tr>
<tr>
<td>WBRT +/- TMZ</td>
<td>Rand. Phase II</td>
<td>Institut Curie (France)</td>
<td>N = 100</td>
</tr>
<tr>
<td>RO4929097 (gamma secretase inhibitor)+WBRT</td>
<td>Phase I/II</td>
<td>MD Anderson</td>
<td>N = 182</td>
</tr>
<tr>
<td>AZD2171 (cedirinib, VEGF inhibitor) + WBRT</td>
<td>Phase I</td>
<td>Mass General/DFCI</td>
<td>N = 12 (multiple)</td>
</tr>
<tr>
<td>ABT-888 (veliparib) + WBRT</td>
<td>Phase I</td>
<td>Abbott (US and Canada)</td>
<td>N = 40 (multiple)</td>
</tr>
<tr>
<td>Vorinostat + WBRT</td>
<td>Phase I</td>
<td>Thomas Jefferson</td>
<td>N = 24 (multiple)</td>
</tr>
</tbody>
</table>

Source: Clinicaltrials.gov and BrainMetsBC.org
Memantine as a Radio-protectant during WBRT: RTOG 0614

Patient Population:
508 patients with Brain metastases
Phase III RCT

WBRT 37.5 Gy in 15 fractions
Plus placebo

Outcomes:
Cognitive Function, Time to cognitive Decline, OS, PFS

Outcomes:
1. Patients in the memantine group experienced a 17% RR in cognitive decline at 24 wks vs. placebo (via HVLT).
2. Trends of all cognitive tests for 149 patients who survived 24 wks showed memantine group yielded better results vs. placebo.
3. No difference in OS or PFS.

* N-Methyl-D-aspartate receptor antagonist

Brown et al. RTOG 0614, ASTRO abstract 2012.
Systemic Therapy for Breast Cancer
Brain Metastases

• When to consider?
  – Recurrent or progressive CNS disease after surgery and/or radiation
  – In patients with minimal CNS disease in setting of significant systemic disease
  – ?? After SRS alone to delay/avoid need for WBRT
    • No prospective data from clinical trials
  – ?? In the highly motivated, informed patient with newly diagnosed brain metastases and limited CNS disease
    • Radiotherapy is the standard, Close follow up necessary

No drugs with FDA approval for systemic treatment of brain metastases
Overview of Systemic Therapies for Breast Cancer Brain Metastases

**Chemotherapy**
- Epothilones, Irinotecan/TMZ, 2B3-101, ANG1005

**Targeted Agents**
- HER2-targeted, VEGF-targeted, Iniparib

**Preclinical**
- mTOR, MEK and PI3K inhibitors
Epothilones

**Patupilone**

- n = 55, of which n = 15 had TNBC
- MOA of Epothilones: Brain penetrant, microtubule stabilizing agents
- Median OS 12.7 mos
- 3 mos PFS, 27% (pre-specified 35%)

**Sagupilone**

- n = 15; n = 1 w/ TNBC; 2 PR's, PFS 1.4 mos; OS 5.3 mos

Peereboom et al. NeuroOnc 2014
Freedman et al. Clinical Breast Cancer 2011
**Study results:**
N = 30, allowed LMDz and all subtypes
3 PR, 3 w/ SD > 6 months – CBR 20%
Median TTP ~ 11.5 weeks

**Melisko et al. ASCO 2009**
2B3-101: PEGylated liposomal anthracycline

5X’s greater brain exposure vs. PLD

Phase I study completed in Europe
Phase II study near completion in the US and Europe
ANG-1005 (GRN-1005)

- Paclitaxel conjugated to Angiopep-2
- Targets the LRP-1 receptor, located at the BBB and up-regulated in brain tumors
- Facilitates receptor-mediated transcytosis across BBB

Thomas et al, Pharm Res 2009  Lin et al.  SABCS 2012, Abstr P3-12-04
**Best overall tumor responses:**
Phase I solid tumors with brain mets, ANG1005-CLN-02

- 5 PRs (24%)
- 10 SDs (48%)

Data from 21 patients dosed at ≥420 mg/m² who received at least 2 cycles of ANG1005 and completed at least 1 post-treatment tumor assessment at ≥6 weeks after the first dose; assessed by investigator per RECIST v1.0.
## Lapatinib

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>CNS ORR</th>
<th>Minor response 20-50% vol</th>
<th>TTP/PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al JCO 2008</td>
<td>39</td>
<td>2.6% (RECIST) 5.2% (50% volumetric reduction)</td>
<td>10%</td>
<td>3.0 mo</td>
</tr>
<tr>
<td>Lin et al CCR 2008</td>
<td>237*</td>
<td>6% (composite criteria)</td>
<td>15%</td>
<td>2.4 mo</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>20% (optional extension)</td>
<td>18%</td>
<td>3.6 mo</td>
</tr>
<tr>
<td></td>
<td>(L+ Cape)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Ongoing/planned Ph II Her2-directed studies:** Everolimus, Vinorelbine, Trastuzumab, Lapatinib + Capecitabine, Neratinib
Primary Endpoint: CNS volumetric response rate (>50% reduction)

**CNS-OR**: 29/43 = 67.4% (95% CI: 52-81)

<table>
<thead>
<tr>
<th>CNS Volumetric change</th>
<th>n = 43 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80% Reduction</td>
<td>9 (20.9)</td>
</tr>
<tr>
<td>50- &lt;80% Reduction</td>
<td>20 (46.5)</td>
</tr>
<tr>
<td>20- &lt;50% Reduction</td>
<td>6 (14)</td>
</tr>
<tr>
<td>&gt; 0- &lt;20% Reduction</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Progression*</td>
<td>6 (14)</td>
</tr>
</tbody>
</table>

NSS improvement: 14/24 = 58.3% (95% CI: 36.6-77.9)

**TTP**: 5.5 months (95% CI = 4.3 – 6mos); **OS**: 6mos survival = 91%

Bachelot et al. Lancet Oncology, 2013;14(1):64-71
Phase II study of everolimus, vinorelbine and trastuzumab in HER2+ breast cancer brain metastases

N=10-36

Screening

Anti-viral therapy for 1-2 weeks if required

Everolimus 5mg PO daily combined with weekly Vinorelbine 25mg/m2 IV and Trastuzumab 2mg/kg2 IV (days 1, 8 & 15)

Clinical assessment Q3 weeks

Baseline brain MRI and QOL assessment &
Obtain archival tissue for correlative studies

Response and QOL assessments (every 9 weeks)

Repeat Cycles3 Until Documented Tumor Progression, OR Unacceptable Toxicity, OR Study Withdrawal, OR Death

Current sites: UNC, Vanderbilt, UAB
23/36 accrued; tissue collection ongoing

1 Required pending results of HBV screening
2 Patients NOT receiving trastuzumab prior to enrollment in the study will receive 4mg/kg as a loading dose on Day 1 of cycle 1 followed by 2 mg/kg weekly for subsequent doses
3 One cycle = 21 days
4 See Section 7.0 and laboratory manual
Other Brain Permeable Her2-targeted agents to keep your eye on….

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company</th>
<th>MOA</th>
<th>Study Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neratinib</td>
<td>PUMA</td>
<td>Oral TKI targeting Her1/Her2</td>
<td>Phase II (TBCRC 022, Freedman)</td>
</tr>
<tr>
<td>ARRY-380 (ONT-380)</td>
<td>Array-Biopharma</td>
<td>Selective HER2 inhibitor</td>
<td>Phase Ib (+ trastuzumab; + TDM1)</td>
</tr>
<tr>
<td>KD019 (XL-647)</td>
<td>Kadmon Corp.</td>
<td>Multi-targeted TKI; Her2 and Src</td>
<td>Phase I w/ trastuzumab</td>
</tr>
</tbody>
</table>
VEGF-inhibition in brain metastases: Safety Data

<table>
<thead>
<tr>
<th>Study(-ies)</th>
<th>Total N</th>
<th>No. pts with brain mets tx’d w/ bevacizumab</th>
<th>CNS hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs</td>
<td>8,443</td>
<td>91 (occult BM)</td>
<td>3.3% grade 4</td>
</tr>
<tr>
<td>ATHENA/SAiL</td>
<td>4,382</td>
<td>321 (occult BM)</td>
<td>0.9% (1 grade 1, 1 grade 3)</td>
</tr>
<tr>
<td>ATLAS/PASSPORT</td>
<td>131</td>
<td>131 (tx’d BM)</td>
<td>0.8% (1 grade 2)</td>
</tr>
</tbody>
</table>

**FDA approved to treat recurrent GBM, May 2009.**
Phase II: Bevacizumab plus carboplatin (+/- trastuzumab) in BCBM

Cohort 1: Her2 neg
Cohort 2: Her2 pos

Her2 neg:
ORR: 67%
PFS: 3.7 mos
OS: 12 mos

Her2 pos:
ORR: 62%
PFS: 6.1 mos
OS: 16 mos

Lin et al. ASCO 2013, Abstr # 513
Phase II study of iniparib with irinotecan to treat pts with TNBC brain metastases

<table>
<thead>
<tr>
<th>Response by Modified RECIST Criteria</th>
<th>Intracranial (n = 34*)</th>
<th>Extracranial (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>4* (12%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13 (41%)</td>
<td>6 (32%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>15 (47%)</td>
<td>12 (63%)</td>
</tr>
<tr>
<td>Clinical Benefit Rate (CR or PR + SD ≥ 6 mos)</td>
<td>9 (27%)</td>
<td>2 (11%)</td>
</tr>
</tbody>
</table>

Survival Statistics:
- TTP: 2.1 mos
- OS: 7.8 mos

*2/4 (50%) with PR with *BRCA1* mutation

Anders et al.  CCR 2010
O'Shaughnessy et al. SABCS 2009
Preclinical Summary Slide: PI3K, MEK and mTOR inhibition

**BKM120 (PI3K inhibition)**

- **C:** Mice with metastases %
  - BRAIN
  - BONE MARROW
  - OVARIAS
  - LUNGS
  - LIVER
  - KIDNEY/ADRENAL
  - BONES
  - OTHER

**Vehicle**

**MEKi + mTORi**

- **Vehicle**
  - BRAIN

**BKM120**

- **Vehicle**
  - BRAIN

Nanni et al. PLOS ONE 2012, 7(6), e39626
Zhao et al. BCRT, March 2011.
UNC/LCCC Multi-disciplinary Brain Metastases Specialty Clinic

Co-Directors

Carey K. Anders, MD
Medical Oncology

Matt Ewend, MD
NSU

Timothy Zagar, MD
Radiation Oncology

Early Phase Clinical Trials
- Local Therapies
- Radiosensitizers
- Systemic Therapy

CNS Metastases Registry
- North Carolina and Surrounding States

Neurocognitive Outcomes
- Onco-psychiatry
- Don Rosenstein

University of North Carolina/LCCC Multi-Disciplinary Brain Metastases Clinic

Prospective Tissue Collection
- Archival FFPE
- Fresh tumor biopsies
- Whole Blood

Faculty Leaders:
- Neurosurgery: Matt Ewend, MD
- Radiation Oncology: Timothy Zagar, MD, Larry Marks, MD
- Medical Oncology: C. Anders, MD, Stergios Moschos MD, Carrie Lee MD

Dedicated Research Coordinators and NP support

Pre-clinical Collaborations
- CCNE collaborators (Zamboni and DeSimone)
- Radiosensitizers (Sambade, Miller)

http://unclineberger.org/brain-metastases/
Conclusions and Future Directions

• Brain Metastases remains a clinical challenge deserving of ongoing research
  – Preclinical models and clinical trials now available

• Subtype specific differences in predilection for CNS recurrence and prognosis are apparent

• Local therapy techniques, including combination radio-sensitization, are rapidly evolving

• Advances in systemic therapies with BBB permeability will lead to improvements in both intra- and extracranial disease
Resources for patients
www.brainmetsbc.org

Invaluable resource which includes information about Brain/CNS metastases, clinical trials, support and stories, ongoing research, scientists and clinicians all determined to make a difference in the treatment of patients with breast cancer and brain metastases.

Thanks and Questions.....