Multidisciplinary management of brain metastases arising from breast cancer

Timothy M. Zagar, MD
Carey Anders, MD

University of North Carolina
Lineberger Comprehensive Cancer Center
Chapel Hill, NC
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Overview

• Background
• What are brain metastases?
• What prognostic factors are important?
• What are the best treatment options?
  – Surgery, whole brain radiation, radiosurgery, chemotherapy
• Future directions
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 limits exposure to chemotherapy

- 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
What is a brain metastasis?

Aka brain met
Not all brain mets are created equal
Bone metastasis, not brain
Leptomeningeal spread
The Blood Brain Barrier

The blood–brain barrier (BBB)

Expert Reviews in Molecular Medicine ©2003 Cambridge University Press
231-BR Brain Metastasis Models for Preclinical Drug Testing

- Intracardiac Injection
- 4 week assay
- Count micrometastases and large metastases

Endpoints:
Prevention  - Prevent development of brain metastases
Treatment   - Shrink or stabilize size of already developed metastases
             - Similar to most clinical trials

Slide courtesy of P. Steeg, PhD
Intracranial Triple Negative Breast Cancer Murine Model

Successive rounds of culture → reinjection of brain metastasis cells → sublines of breast cancer cell lines that hone to CNS/bone

MDA-MB-231 (Br) and (Bo)

Yoneda et al. J Bone Min Res, 2001
Subtype-Specific Patterns of Metastases
Breast cancer brain mets ≠ other cancer brain mets

• Most of the data in brain metastases is from patients with ALL types of cancer → breast patients are clearly different than lung cancer patients for example

• Extrapolating data from old trials is a problem
Other prognostic factors

- Age
- Performance status
- Status of other disease outside the brain
- Number of brain metastases
Symptoms

• Headache
• Focal neurologic dysfunction
  – E.g. Weakness on one side
• Cognitive dysfunction
  – “not myself,” problems concentrating
• Stroke
• Seizures
What are treatment options?

• Supportive care
  – Steroids
  – Antiepileptics

• Whole Brain Radiation Therapy (WBRT)

• Local Therapy
  – Surgical Resection
  – Stereotactic Radiosurgery (SRS)

• Combination of Local Therapy and WBRT
  – Surgery followed by WBRT or SRS
  – WBRT followed by Surgery or SRS
  – SRS followed by WBRT

• Systemic Therapy (Chemotherapy, Targeted Agents)
Whole brain radiation
Whole brain radiation

- Treats the whole brain, not just the diseased areas
  - decreases chances of developing new areas
- Sounds good, right?
Whole brain radiation

- FATIGUE
- Hair loss

- Neurocognitive dysfunction
  - Trouble with short term memory
  - In old days → Alzheimer’s like dementia
  - Namenda (memantine)?
Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial

- N=113
- 3000 cGy
- 4 months Hopkins Verbal Learning Test- Revised Delayed recall
- 7% decline, better than historical data
Is there a radiation alternative to whole brain radiation?

• The answer is “yes”…

• In select cases
Radiosurgery

CyberKnife for brain metastases
High dose: 1 to 5 fractions

- Radiosurgery delivers high radiation doses to precise locations
- Accomplished with advanced technology
CyberKnife

- Deliver radiosurgery accuracy without requiring the harsh restraints
CyberKnife

- The CK is built on a KUKA robot
- This gives great flexibility in beam direction
Lots o’ beams
Dose conformality

- This allows great flexibility in beam direction
- Improved conformality becomes possible
- Less “normal” brain treated → less neurocognitive decline (we think)
Radiosurgery

- Less fatigue
- Usually no hair loss
- Often can go on to receive chemotherapy faster than after whole brain radiation
- Risk of radiation necrosis requiring neurosurgery
CyberKnife Treatment Planning
Conclusions

• CyberKnife delivers high doses with sub-millimeter accuracy to patients

• Only light patient immobilization

• Sounds great…so why doesn’t everyone get it?
Radiosurgery drawbacks

• Can only do for a “few” metastases
  – Risk of radiation necrosis increases the more you treat

• CyberKnife (or any other method of delivering radiosurgery) only works where we point it
  – Non-treated areas are still at risk for developing new metastases
More than 1

• “Low” dose radiation spill

• The more areas targeted, the more potential for dose overlap
  – Risk of radiation necrosis
Radiotherapy Treatment Options

- Better “distant” whole brain microscopic disease control
- Avoid side-effects of WBRT
- Availability of salvage treatments
- Risk of long-term neurotoxicity and side-effects
- Negative impact of tumor progression

<table>
<thead>
<tr>
<th>WBRT</th>
<th>SRS</th>
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</table>
| • Many mets (cutoff?)  
• Poor performance status  
• RPA class  
• Histology (SCLC) | • Few mets  
• Good performance status  
• Low RPA |
Neurosurgery
What about surgery?

- Often when there is 1 metastasis (rarely 2)
- When symptomatic
- When diagnosis is in question

- Not enough—need more treatment after resection
When do we consider systemic therapy to treat brain metastases?
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
    • No drugs with FDA approval for systemic treatment of brain metastases
Overview of Systemic Therapies for Breast Cancer Brain Metastases

Chemotherapy
- Epothilones, Irinotecan/TMZ, Carrier-mediated agents (2B3-101, ANG1005)

Targeted Agents
- HER2-targeted (namely Lapatinib), Parp Inhibitors (Veliparib), CDK4/6 inhibitors (abemaciclib)

Preclinical
- mTOR, MEK and PI3K inhibitors and beyond!
2B3-101: PEGylated liposomal anthracycline

5X’s greater brain exposure vs. Doxil®

Phase I study completed in Europe
Phase II study near completion in the US and Europe

Personal communication, to-BBB 2013
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
Phase II study of everolimus, navelbine and trastuzumab in HER2+ breast cancer brain metastases

**SCREENING**

- Anti-viral therapy for 1-2 weeks if required

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

- Response and QOL assessments (every 9 weeks)

- Clinical assessment Q3 weeks

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

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

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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
Consent and Screening (n = 60)

Baseline brain MRI (≥ 1 measurable lesion)
CT Chest/Abdomen/Pelvis, CTCs

Neratinib (240 mg orally once daily) and capecitabine 750 mg/m² BID for 14 days followed by 7 days rest

Follow-up every 3 weeks

Brain MRI & body CT re-staging at week 6

CR, PR, SD – Continue therapy

PD (CTCs)
• If CNS PD – Off study
• If non CNS PD – extension with trastuzumab offered

Re-stage every 2 cycles while on study until 18 weeks, then re-stage every 3 cycles

Diarrhea ppx, RN phone call 24, 48, 72 hours

No prior lapatinib (cohort 3a) n=35

Prior lapatinib (cohort 3b) n=25

Courtesy of PI: Rachel Freedman, MD
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>
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</thead>
<tbody>
<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>
<tr>
<td>TDM1 (??)</td>
<td>Genentech</td>
<td>Trastuzumab conjugated to Emtansine</td>
<td>Phase II in development</td>
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A Phase 2 Study of Abemaciclib in Patients With Brain Metastases Secondary to Hormone-Receptor-Positive Breast Cancer

Patients with brain metastases secondary to HR+ breast cancer

Part A: HER2-positive; 200 mg abemaciclib PO Q12H*

Part B: HER2-negative; 200 mg abemaciclib PO Q12H*

Part C: HER2-positive or HER2-negative; 200 mg abemaciclib PO Q12H 5-14 days prior to surgical resection**

Primary Endpoint: Objective intracranial response rate

* Participants continue study treatment until development of progressive disease, unacceptable toxicity, or withdrawal.
** Dosing may resume after wound healing period.
Preclinical Summary Slide:
PI3K, MEK and mTOR inhibition

BKM120 (PI3K inhibition)

Vehicle      BKM120

Vehicle      MEKi + mTORi
QUESTION:

Can we use systemic therapies to protect un-irradiated brain from metastases following radiation therapy?
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

http://unclineberger.org/brain-metastases/

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

Novel Neuroimaging
BRIC (Yueh Lee)
Keith Smith, MD

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)
BCBM Specialty Clinic at UNC

• Clinic is held every Wednesday morning
  – Radiation Oncology Department in the NCCH
  – Contact: 1-919-445-5295

http://unclineberger.org/brain-metastases
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.
• Thank you!

• Questions?