Brain metastases in HER2 positive breast cancer patient resistant to trastuzumab and lapatinib

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Centre Léon Bérard, Lyon
Better prognosis of patient with HER2+ve MBC and brain metastasis

Old series: 6 month median

New series: > 12 months

Current guidelines'

NCCN Guidelines™ Version 2.2011
Multiple (>3) Metastatic Lesions

- WBRT

NCCN Guidelines™ Version 2.2011
Limited (1-3) Metastatic Lesions

Disseminated disease
Poor systemic options

- WBRT

Newly dx’d or stable systemic dz,
Or reasonable systemic options

unresectable

- WBRT and/or SRS

resectable

- Surg or SRS and/or WBRT
Brain metastasis and systemic therapy

- In theory, Blood-brain barrier (BBB) isolates CNS from systemic treatment
Brain metastasis and systemic therapy

- But BBB is altered in neovasculature, particularly in the case of metastatic disease

Tumoral paclitaxel concentration
## Brain metastasis from breast cancer: Upfront systemic therapy

<table>
<thead>
<tr>
<th>Ref</th>
<th>Treatment</th>
<th>Theoretical BBB permeability</th>
<th>N</th>
<th>ORR</th>
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<tbody>
<tr>
<td>Rosner et al. Cancer 1986</td>
<td>Endoxan + 5-FU +/- MTX</td>
<td>No Limited</td>
<td>87</td>
<td>53%</td>
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<tr>
<td>Boogerd et al. Cancer 1992</td>
<td>CMF CAF</td>
<td>Limited Limited</td>
<td>22</td>
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<td>CDDP + VP16</td>
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<td>Trudeau et al. Ann Oncol 2006</td>
<td>Temozolomide</td>
<td>Yes</td>
<td>18</td>
<td>0 %</td>
</tr>
<tr>
<td>(5 with BM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivera Cancer 2006</td>
<td>Temozolomide + lapatinib</td>
<td>Yes Limited</td>
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Brain metastasis from breast cancer: Upfront systemic therapy

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=> *Response is related to intrinsic drug activity against BC, not BBB permeability*
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<th>CNS Volumetric change</th>
<th>n</th>
<th>(%)</th>
</tr>
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<tbody>
<tr>
<td>≥ 50% Reduction</td>
<td>29</td>
<td>65.9%</td>
</tr>
<tr>
<td>20- &lt;50% Reduction</td>
<td>6</td>
<td>13.6%</td>
</tr>
<tr>
<td>&gt; 0- &lt;20% Reduction</td>
<td>2</td>
<td>4.5%</td>
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<th>RECIST response rate</th>
<th></th>
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<tr>
<td>CNS disease</td>
<td>24/42</td>
<td>57.2%</td>
</tr>
<tr>
<td>Extra CNS disease</td>
<td>15/34</td>
<td>44.1%</td>
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Bachelot et al, ASCO 2011
EGF105084 - Lapatinib plus Capecitabine Extension Phase. N=50

Eligibility: prior trastuzumab therapy and cranial RT, HER2+, radiographic evidence of brain metastases, ECOG PS=0-2

Parent Study

Lapatinib monotherapy 1500mg/day

Extension Arm

Lapatinib 1250 mg/day + capecitabine 2000 mg/m²/day 14 of 21 days

Study objectives: CNS ORR(CR+PR rate), site of first progression, PFS, tolerability, percentage of patients with ≥20% volumetric reduction in brain lesions

### Cape + Lapa after WBRT and Lapa alone, N=50

<table>
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<tr>
<th>Best Response</th>
<th>Patients, N (%)</th>
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<tbody>
<tr>
<td>CR*</td>
<td>0</td>
</tr>
<tr>
<td>PR*</td>
<td>10 (20)</td>
</tr>
<tr>
<td>SD</td>
<td>20 (39)</td>
</tr>
<tr>
<td>PD</td>
<td>15 (29)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (12)</td>
</tr>
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*CNS composite objective response (CR and PR) requiring:
- no new or progressive non-CNS lesions,
- no increase in steroid requirement, or
- worsening of neurologic sign or symptoms.

Duration of CNS tumor regression for patients with ≥ 20% reduction
Other nice results from other tumor type and un-approved treatment

Angiogenesis inhibitor

Complete Response of Brain Metastasis With Sunitinib in Metastatic RCC

Onset 3 months-durable through month 21+

Other nice results from other tumor type and un-approved treatment

Iressa on brain metastases from NSCLC with EGF mutation after WBRT

Cappuzzo et al., Lung Cancer 2003; 41, 227–231
What to do for a HER2 positive breast cancer patient with Brain metastases resistant to trastuzumab and lapatinib?

- All possible radiotherapy
- Clinical trial of new targeted therapy
- Any breast cancer active chemotherapy
Case Study

- 55 year old, no pathology
- 08-2008: Discover a right breast lump
- Biopsy: ER 70%++; PR-, HER2+++
- CT scan: Liver and bone metastasis

⇒ Trastuzumab/paclitaxel
⇒ 02-2009 : complet remission; no surgery
Case Study

- 06-2009: headache => MRI: 3 brain mets

⇒ Inclusion in LANDSCAPE study: Capecitabine and lapatinib (C+L)
Case Study

- 09-2009: Good PR, no more symptom
Case Study

- 11-2009: Progression, multiples new brain lesion, no extra CNS progression

WBRT

Trastuzumab and Letrozol
Case Study

- For 1 year:
  - No cerebral progression
  - No local progression
  - No liver progression
  - 1 active bone metastasis: RDT
Case Study

- 11-2010: New unique cerebellum met
- No extra CNS progression

SRS
Case Study

- 06-2011: New unique brain progression
- No extra CNS progression

SRS bis
Case Study

- 06-2012: New cerebellum localization
- No extra CNS progression

AFATINIB vs. Whatever

Trastu Vinorelbine
Case Study

- At the present time: Stable disease
- No extra CNS progression

What next?