Brain metastases (BM): New techniques and place of targeted systemic treatments

Prof. Rafal Dziadziuszko
Medical University of Gdańsk, Poland

SAMO, Lucerne, January 25, 2014
Treatment options for NSCLC patients with brain metastases

- Whole brain radiotherapy (WBRT)
- Stereotactic radiotherapy
- Surgery
- Chemotherapy
- Targeted therapies
- Best supportive care
## Stratification of cancer patients with brain metastases

**RPA classes I - III**

<table>
<thead>
<tr>
<th>KPS≥70</th>
<th>Age&lt;65 and Controlled primary site and No mets outside CNS</th>
<th>7.1 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS ≥ 70</td>
<td>Primary site active and/or Mets outside CNS present Age ≥ 65</td>
<td>4.2 months</td>
</tr>
<tr>
<td>KPS&lt; 70</td>
<td></td>
<td>2.3 months</td>
</tr>
</tbody>
</table>

Gaspar IJROBP 1997;37:745-751
Stratification of cancer patients with brain metastases

Gaspar IJROBP 1997;37:745-751
Stratification of cancer patients with brain metastases: Graded Prognostic Assessment (GPA) Score

<table>
<thead>
<tr>
<th>Non–small-cell and small-cell lung cancer</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic Factor</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Age, years</td>
<td>&gt; 60</td>
<td>50-60</td>
</tr>
<tr>
<td>KPS</td>
<td>&lt; 70</td>
<td>70-80</td>
</tr>
<tr>
<td>ECM</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>No. of BM</td>
<td>&gt; 3</td>
<td>2-3</td>
</tr>
<tr>
<td>Sum total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median survival (months) by GPA: 0-1.0 = 3.0; 1.0-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

<table>
<thead>
<tr>
<th>Melanoma</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic Factor</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>KPS</td>
<td>&lt; 70</td>
<td>70-80</td>
</tr>
<tr>
<td>No. of BM</td>
<td>&gt; 3</td>
<td>2-3</td>
</tr>
<tr>
<td>Sum total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

<table>
<thead>
<tr>
<th>Breast cancer</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic Factor</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>KPS</td>
<td>≤ 50</td>
<td>60</td>
</tr>
<tr>
<td>Subtype</td>
<td>Basal</td>
<td>n/a</td>
</tr>
<tr>
<td>Age, years</td>
<td>≥ 60</td>
<td>&lt; 60</td>
</tr>
<tr>
<td>Sum total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

<table>
<thead>
<tr>
<th>Renal cell carcinoma</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic Factor</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>KPS</td>
<td>&lt; 70</td>
<td>70-80</td>
</tr>
<tr>
<td>No. of BM</td>
<td>&gt; 3</td>
<td>2-3</td>
</tr>
<tr>
<td>Sum total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8

<table>
<thead>
<tr>
<th>GI cancers</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic Factor</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>KPS</td>
<td>&lt; 70</td>
<td>70</td>
</tr>
</tbody>
</table>

Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.8; 4.0 = 13.5

Sperduto JCO 2012;30:419-425
Stratification of NSCLC patients with brain metastases: Graded Prognostic Assessment (GPA) Score

Sperduto JCO 2012;30:419-425
Stratification of NSCLC patients with brain metastases: Graded Prognostic Assessment (GPA) Score

Median OS according to treatment of NSCLC patients with brain metastases (months)

<table>
<thead>
<tr>
<th>WBRT</th>
<th>SRS</th>
<th>WBRT+SRS</th>
<th>S+SRS</th>
<th>S+WBRT</th>
<th>S+WBRT+SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.53</td>
<td>9.86</td>
<td>12.72</td>
<td>11.86</td>
<td>11.66</td>
<td>12.06</td>
</tr>
</tbody>
</table>

Sperduto JCO 2012;30:419-425
NSCLC Patients with 1-3 metastases: Indications for surgery vs. SRS

<table>
<thead>
<tr>
<th>Surgery</th>
<th>SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single lesions</td>
<td>Smaller lesions</td>
</tr>
<tr>
<td>Larger lesions w/mass effect</td>
<td>Multiple lesions (1 – 3?)</td>
</tr>
<tr>
<td>Outside „vulnerable” surgical areas</td>
<td>All locations in the brain, including brain stem</td>
</tr>
<tr>
<td>No contraindications to surgery</td>
<td>Patients who are not surgical candidates</td>
</tr>
</tbody>
</table>
Key evidence: WBRT vs. SRS + WBRT
RTOG 9508 trial (N=331)

• 1-3 metastases, < 40 mm
• WBRT 37.5 Gy/15 fx
• Local control 71% vs 82%; p<0.05
• Overall survival 6.5 vs 5.7 months; NS
• Subset of pts with single metastasis:
  OS 4.9 vs 6.5 months; p<0.05
• 6-month KPS improvement and steroid intake favors SRS+WBRT

Andrews DW Lancet 2004
Key evidence: WBRT vs. SRS + WBRT
RTOG 9508 trial – 2013 GPA update

• 252/331 patients re-analyzed according to GPA

Median OS according to treatment arm and GPA score

<table>
<thead>
<tr>
<th>GPA &lt; 3.5 (N=205)</th>
<th>WBRT</th>
<th>WBRT+SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.4</td>
<td>5.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GPA = 3.5 – 4.0 (N=47)</th>
<th>WBRT</th>
<th>WBRT+SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10.3</td>
<td>21.0</td>
</tr>
</tbody>
</table>

Sperduto et al., ASTRO 2013: abstr 123
Key evidence: Surgery / SRS with or without WBRT
EORTC 22952-26001 trial (N=359)

- 1-3 brain metastases <30 mm
- Disease control outside CNS
- WHO PS 0-2
- Randomizations after surgery or SRS: WBRT vs observation
- WBRT 30 Gy/10 fr

Kocher M JCO 2011
Key evidence: Surgery / SRS with or without WBRT
EORTC 22952-26001 trial (N=359)

Kocher M JCO 2011
Key evidence: Surgery / SRS with or without WBRT
EORTC 22952-26001 trial (N=359)

Kocher M JCO 2011
WBRT: Cognitive function deficit

Figure 2: Prior and posterior distributions of probability of cognitive decline (5 points or greater fall from baseline) assessed by HVLT-R (total recall)

Chang et al., Lancet 2009
Surgery and SRS: Summary

- Should be considered in selected good prognosis patients with 1 - 3 brain metastases
- SRS improves survival when added to WBRT in patients with single metastasis / GPA 3,5 - 4
- WBRT improves local control but not survival when added to surgery or SRS
- WBRT associated with moderate cognitive disfunction
- In most patients with GPA 3,5 - 4: consider surgery or SRS without WBRT, particularly if effective systemic tx exist
New approaches

• Hippocampal-sparing RT
• Whole brain radiotherapy (WBRT) with simultaneous integrated boost (SIB) to BM
• Brain protective agents
Hippocampal-sparing RT
Hippocampal-sparing RT

• Injury of the neuronal stem cells located in the granular cell layer of the hippocampus correlates with neurocognitive decline in preclinical models

• Hippocampal-sparing RT appers safe (involvement of hippocampal structures <3% of patients, more common in SCLC than in NSCLC)

• Modeling study shows 0.2% - 4% increase in risk of brain failure after hippocampal-sparing RT (NSCLC and SCLC, respectively)

Involvement of perihippocampal region:
3% of metastases; 8% of patients

Gondi V et al. Radiother. Oncol. 2010
Hippocampal-sparing RT

Contouring guidelines from RTOG 0933 trial
http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0933

Shaw MG, Ball DL. Curr Treat Options Oncol 2013; 14: 553
Hippocampal-sparing RT: RTOG 0933
(N=113, closed to accrual, single arm phase II)

**Primary endpoints:**
- Evaluate delayed recall as assessed by the Hopkins Verbal Learning Test-Revised (HVTL-R) at 4 months after hippocampal avoidance during whole-brain radiotherapy (HA-WBRT) in patients with brain metastasis.

**Secondary endpoints:**
- Evaluate auditory and visual learning and memory, as assessed by 2 CogState tests (International Shopping List Test and One Card Learning Test), after HA-WBRT in these patients.
- Compare psychometric properties of the 2 CogState tests to the HVLT-R for the assessment of memory decline after HA-WBRT in these patients.
- Evaluate health-related quality of life [as assessed by the Functional Assessment of Cancer Therapy with Brain Subscale (FACT-BR) and the Barthel Index of Activities of Daily Living (ADLs)] after HA-WBRT in these patients.
- Evaluate time to radiographic progression after HA-WBRT in these patients.
- Evaluate overall survival of these patients after HA-WBRT.
- Evaluate the adverse events of HA-WBRT.
- Evaluate predictive biomarkers of cognitive function.

http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0933
Hippocampal-sparing RT: Controversies

- Elevated risk of brain failure due to inadequate coverage of perihippocampal region?
- Is dose to hippocampus <8-10 Gy adequately low to prevent neurocognitive deficits?
- Will reduced neurocognitive deficit indeed be observed - neuronal stem cells are located also outside of hippocampal structures?
WBRT with dose escalation to BM
WBRT with dose escalation to BM

- Phase I dose escalation trial (N=48) in patients with 1-3 BM from different primary tumors
- WBRT = 30Gy / 10fr + dose escalation (SIB): 35Gy, 45Gy, 50Gy, 55Gy, 60Gy
- Treatment was given with tomotherapy
- SIB dose of 60Gy was feasible and well tolerated
- Several phase II trials are planned / ongoing

Rodrigues et al. Radiat Oncol 2012; 7: 42
WBRT with dose escalation to BM

Example of RT dose distribution using volumetric arc radiotherapy

Neuroprotective agents
Neuroprotectors currently evaluated in patients treated with brain RT

- **Memantine** = N-methyl-D-aspartate (NMDA) receptor antagonist used in vascular and Alzheimer’s dementia
- **Donepezil** = acetyl cholinesterase inhibitor used in Alzheimer’s dementia
- **Lithium carbonate** = mood stabilizer used in bipolar disorder
- **Renin angiotensin system blockers** (ramipril)
- **Peroxisomal proliferator-activated receptor (PPAR) agonists** (pioglitazone)

Shaw MG, Ball DL Curr Treat Options Oncol 2013; 14:553-567
Memantine during and after WBRT (37 Gy/15 fx)

Memantine as neuroprotector during WBRT

Does targeted therapy change the BM landscape in NSCLC?
Targeted therapies and BM

• Targeted therapies are more effective than chemotherapy in specific subsets of NSCLC patients
• Pharmacokinetic properties of targeted agent in relation to blood-brain barrier (BBB) are extremely important
• Better systemic control with targeted agents may significantly prolong survival of NSCLC patients with BM and influence the prognostic scoring systems
Pharmacokinetic brain relapse

• ALK+ NSCLC has propensity for early brain dissemination (~30% of pts participating in PROFILE 07 trial)

• Crizotinib penetration to CSF <1%

• Many “progressions” occur exclusively in the CNS (brain, meninges, spinal cord) - pharmacokinetic relapses

• With continued systemic control, serial CNS imaging is warranted while on crizotinib to institute WBRT and/or SRS early, possibly disrupt BBB and prevent neurologic symptoms
ALK+ patients and BM
Gdansk experience

BM=brain metastasis; BP=brain progression; SP=systemic progression; WBRT=whole brain RT
Miliary brain metastases in a patient with *ROS1* rearrangement

After 6 months on crizotinib

After WBRT and another 4 months on crizotinib

Dziadziuszko K, J Thorac Oncol, in press
Efficacy of EGFR tyrosine kinase inhibitors (TKIs) in patients with brain metastases

Table 1. Trials studying the efficacy of EGFR tyrosine kinase inhibitors in non-small cell lung cancer with central nervous system metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Selection</th>
<th>Phase</th>
<th>N</th>
<th>RR (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unselected patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceresoli et al. (51)</td>
<td>Gefitinib</td>
<td>European</td>
<td>II</td>
<td>41</td>
<td>27</td>
<td>PFS 3 mo</td>
</tr>
<tr>
<td>Wu et al. (52)</td>
<td>Gefitinib</td>
<td>East Asian, adenocarcinoma</td>
<td>II</td>
<td>40</td>
<td>32</td>
<td>PFS 9 mo</td>
</tr>
<tr>
<td>Selected patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hotta et al. (53)</td>
<td>Gefitinib</td>
<td>East Asian</td>
<td>II</td>
<td>57</td>
<td>43</td>
<td>OS 12.9 mo</td>
</tr>
<tr>
<td>Porta et al. (54)</td>
<td>Erlotinib</td>
<td><em>EGFR</em> mutation</td>
<td>II</td>
<td>69</td>
<td>82</td>
<td>OS 12.9 mo</td>
</tr>
<tr>
<td>Kim et al. (55)</td>
<td>Gefitinib or</td>
<td><em>EGFR</em> mutation, East Asian, adenocarcinoma</td>
<td>II</td>
<td>23</td>
<td>70</td>
<td>PFS 6.6 mo, OS 19.8 mo</td>
</tr>
<tr>
<td></td>
<td>erlotinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al. (41)</td>
<td>Gefitinib</td>
<td><em>EGFR</em> mutation, East Asian</td>
<td>II</td>
<td>110</td>
<td>89</td>
<td>PFS 7.1 mo, OS 18.8 mo</td>
</tr>
<tr>
<td>Wu et al. (57)</td>
<td>Erlotinib</td>
<td>East Asian, <em>EGFR</em> mutation, and/or adenocarcinoma</td>
<td></td>
<td>48</td>
<td>56</td>
<td>PFS 23.2 mo</td>
</tr>
<tr>
<td>Kim et al. (60)</td>
<td>Gefitinib or</td>
<td>East Asian, never-smoker, adenocarcinoma</td>
<td>II</td>
<td>23</td>
<td>74</td>
<td>PFS 7.1 mo, OS 18.8 mo</td>
</tr>
<tr>
<td></td>
<td>erlotinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: mo, months; OS, overall survival; PR, partial response; RR, response rate; TTP, time to progression.
EGFR TKIs for tx of brain metastases in patients w/ EGFR mutated tumors

- 28 NSCLC patients with NSCLC and brain mets
- Phase II study with either gefitinib or erlotinib
- RR = 83%, median PFS = 6.6 months, median OS = 15.9 months

Park SJ et al., Lung Cancer 2012
Pharmacokinetics of EGFR inhibitors in NSCLC 15 patients w/EGFR mutant tumors and brain metastases

<table>
<thead>
<tr>
<th></th>
<th>Mean concentration</th>
<th>CSF penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>3.7ng/mL</td>
<td>1.13%</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>28.7ng/mL</td>
<td>2.77%</td>
</tr>
</tbody>
</table>

Togashi Y et al., Cancer Chemother Pharmacol 2012
CNS progression on EGFR or ALK inhibitors

- Mechanism could be pharmacokinetic
- In a gefitinib treated patient, consider switch to erlotinib to achieve higher CSF concentrations
- Several retrospective series demonstrate some efficacy of erlotinib pulse-dosing, e.g. erlotinib 300mg every other day or erlotinib 600mg every 4 days
- Similar observation of efficacy of crizotinib pulse-dosing (500mg OD) was published in ALK+ NSCLC
Can I treat brain metastases in NSCLC EGFR mut patient with WBRT and concurrent erlotinib/gefitinib?

- Most small series data indicate no significant toxicity of concurrent tx;
- However few case reports with significant toxicity are published
- Comparative clinical trial is ongoing
- Before the results of the trial become available, I prefer to give WBRT and temporaarily stop erlotinib or gefitinib
**Quizz**

- 60 y.o. white female w/metastatic lung adenocarcinoma who progressed 3 months after completing PEM/CIS 1. line chemotherapy: enlargement of lung primary, supraclavicular nodes and new symptomatic BMs (5 lesions, largest: 3 cm)

- Molecular genotyping showed **HER2** exon 20 insertion (YVMA)

- What next?
  - WBRT?
  - Paclitaxel/trastuzumab weekly?
  - Afatinib?
  - Docetaxel/trastuzumab q 3 weeks?
  - Lapatinib?
Quizz

- Patient received WBRT (30Gy/15fx) and paclitaxel 70mg/m2 weekly + trastuzumab 2mg/kg weekly after starting dose of 4mg/kg
- Stable disease in the brain at 8 months
- Partial response in extracranial sites at 8 months
- Patient fully ambulatory, returned to work
Take-home messages

• Stratification of BM patients according to prognostic models is important
• WBRT remains the standard of care in most patients
• Surgery or SRS should be considered in selected good prognosis patients with 1–3 brain metastases; WBRT may be deferred in these patients until progression in the brain
• Targeted therapies can prolong survival of NSCLC patients with BM. I usually use WBRT in such patients prior to targeted agent if BBB penetration is poor.
Thank you for your attention!