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Treatment of Brain Metastases in 2015: Are Kinase Inhibitors Useful?

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Disclosures

Eisai and Novartis - consulting
Outline

• Background
• Treatment modalities
• Targeted therapies
• Future studies
Background: Brain Metastases (BM)

- Brain is the most common site of CNS metastases
- Incidence = >150,000 cases per year
- 20% - 40% of cancer patients will develop brain metastases/year
- Median survival without treatment < 2 months
- In RCC BM rarely occur without extracranial metastases
Goals of management

**Short term**
- Stabilize CNS symptoms
- Prevent neurologic deterioration
- Address emergencies: status epilepticus, significant mass effect, acute hydrocephalus and hemorrhage
- Determine extent of CNS and systemic involvement

**Long term**
- Preserve cognitive function
- Systemic treatment
- Improve survival
- Minimize side effects
- Safety
Management choices include

• Surgery
• Radiotherapy (WBRT, radiosurgery)
• Systemic therapy (i.e. TKIs)
• No treatment of CNS disease
  -ignore minimal disease
  -palliative care
Why Perform Surgery for Brain Metastases?

- Establish tissue diagnosis
- Improve mass effect/edema
- Definitive therapy for the local disease
- No radiation necrosis
- Improve quality of life
- Improve overall survival
Resection + WBRT improves survival

Patchell et al (NEJM 1990) n=48

Table 1. Patients’ Characteristics.

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>SURGERY GROUP (N = 25)</th>
<th>RADIATION GROUP (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>18/7</td>
<td>14/9</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td>Range</td>
<td>44–74</td>
<td>49–73</td>
</tr>
<tr>
<td>Karnofsky score (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Range</td>
<td>70–100</td>
<td>70–100</td>
</tr>
<tr>
<td>Primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung (non-small-cell)</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Similarly, Vecht et al (Ann Neurol 1993) n=63

Median OS 12 vs. 7 months (more pronounced in patients with stable extracranial disease)

- Local recurrence rate reduction 52% to 20%
- Median OS 40 vs. 15 weeks
- Better quality of life
SRS for Brain Metastasis from RCC

Stereotactic radiosurgery for patients with multiple brain metastases (JLGG0901): a multi-institutional prospective observational study


Stereotactic Radiosurgery for Brain Metastasis from Renal Cell Carcinoma

Yoshinori Higashi, et al.


BACKGROUND: The authors evaluated the results after stereotactic radiosurgery (SRS) for brain metastases from renal cell carcinoma (RCC) and identified factors associated with improved survival and tumor control.

METHODS: The authors reviewed the management results from a total of 32 RCC brain metastases in 35 consecutive patients who underwent stereotactic radiosurgery (SRS) during a 5-year period. Twenty-five patients also underwent whole brain radiation therapy (WBRT). The mean tumor volume was 2.6 ml (range, 0.1-13.1 ml). The mean dose delivered to the tumor margin was 17 gray (Gy) (range, 12.2-29 Gy). Univariate and multivariate analyses were performed to determine significant prognostic factors.

RESULTS: Although the total number of metastases was small, results showed that radiation dose was significantly associated with improved survival. Median overall survival was 13.9 months (range, 2.8-39 months).

CONCLUSIONS: SRS is an effective treatment for RCC brain metastasis. A higher radiation dose is associated with improved survival.
What about systemic therapy for RCC?

Some of the challenges include:

• Blood brain barrier?
• Limited data on Efficacy and Safety?
• Prognostic Factors?
Blood brain barrier (BBB) excludes most chemotherapy. What about TKIs?

- Accumulation of TKIs in the brain may be reduced by ATP-binding cassette (ABC) drug efflux transporters (P-gp and BCRP) [Tang et al. *Int J Cancer* 2012]

- Preclinical data suggests limited penetration of sorafenib/sunitinib into normal brain tissue [Dudek et al. *Clinical Genitourinary Cancer*, 2013]

- Brain penetration of sunitinib may reach 31% in animal studies vs. 1% to 10% by other TKIs [Hu et al. *Clin Cancer Res*, 2009]
## Efficacy and safety of TKIs in brain metastases: Expanded Access Programs (EAP)

### Sunitinib (Gore et al. *Lancet Oncol* 2009): n=213

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>26 (12%)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>PR</td>
<td>25 (12%)</td>
</tr>
<tr>
<td>SD</td>
<td>111 (52%)</td>
</tr>
<tr>
<td>PD</td>
<td>76 (36%)</td>
</tr>
</tbody>
</table>

Median PFS 5.6 mo; OS 9.2 mo

### Sorafenib (Stadler et al. *Cancer* 2010): n=50

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>SD</td>
<td>34 (68%)</td>
</tr>
<tr>
<td>PD</td>
<td>14 (28%)</td>
</tr>
</tbody>
</table>

CR+PR+SD 36 (72%)

Clinically acceptable toxicity profile
Phase II Trial of Sunitinib in Patients with RCC and Untreated Brain Metastases [Chevreau et al. Clin Genitourin Cancer 2014]

- Measurable (more than 2 cm) and inoperable brain metastases (BM)
- No prior treatment for brain met
- **Primary endpoint** was objective response in BM after 2 cycles

Adapted from Chevreau et al. Clin Genitourin Cancer 2014

<table>
<thead>
<tr>
<th>Previous Nephrectomy</th>
<th>7 (41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear-Cell Carcinoma</td>
<td>16 (94)</td>
</tr>
<tr>
<td>ECOG PS 0-1</td>
<td>14 (88)</td>
</tr>
<tr>
<td>MSKCC Intermediate or Poor Risk</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Corticosteroid Therapy</td>
<td>12 (75)</td>
</tr>
<tr>
<td>Median Number of CNS Metastases (Range)</td>
<td>1 (1-4)</td>
</tr>
</tbody>
</table>
Phase II Trial of Sunitinib in Patients with RCC and Untreated Brain Metastases [Chevreau et al. Clinical Genitourinary Cancer 2014]

Time to Progression

- Median, 2.3 months, 95% CI, 1.2-5.4

Overall survival

- 1 CR (outside of CNS)
- 5 SD (31%)

Remainder of data is limited to retrospective studies
Prognostic factors


- Class 1: KPS ≥ 70%, controlled systemic disease, age <65 years, and metastases to the brain only. Median survival, 7.1 months
- Class 3: KPS < 70%. Median survival, 2.3 months
- Class 2: all others. Median survival 4.2 months
Prognostic factors of survival in patients with mRCC with BM treated with targeted therapy


- 106 patients
  - 47 with BM at presentation
  - 59 with BM during targeted tx
- Heng criteria
  - 12% Favorable
  - 42% Intermediate
  - 29% Poor
- 37% had KPS <80%
- 80% had neurologic symptoms at presentation

<table>
<thead>
<tr>
<th>Treatment received, No (%)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>77 (72.6)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>22 (21.6)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>5 (4.7)</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment of BM, No (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td>86 (81.1)</td>
</tr>
<tr>
<td>SRS</td>
<td>22 (24.8)</td>
</tr>
<tr>
<td>Surgery</td>
<td>27 (25.5)</td>
</tr>
</tbody>
</table>
Results from the International Metastatic Renal Cell Carcinoma Database Consortium

Prognostic factors of overall survival

• KPS<80%
• Diagnosis to treatment with targeted therapy <1 year
• Higher number of brain metastases (>4)
  • OS for ≤ 4 BM was 15.4 vs. 3.9 for >4 BM (p=.0051)
Expert Recommendation for First-line Management of Metastatic RCC in Special Subpopulations. [Puente et al, Targ Oncol 2016]

• Sunitinib has the greatest body of evidence
• Local therapy is of paramount importance
• Propose the following algorithm
Multidisciplinary Approach
What’s on the horizon?

- Immunotherapy studies
  - Phase 3b/4 Safety Trial of Nivolumab in Subjects With Advanced or Metastatic Renal Cell Carcinoma (CheckMate 374) (NCT02596035)
  - Nivolumab in Symptomatic Brain Metastases (CA209-322) (NCT02621515)

- Immunotherapy plus radiation therapy
  - Studies in NSCLC and melanoma
Thank you
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