Leptomeningeal Carcinomatosis: Risks, Detection, and Treatment

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May 13, 2016
Disclosures

- None to declare
Outline

- Epidemiology of brain metastases
- Mechanisms of leptomeningeal spread
- Investigations
- Treatment options
- Moving forward: opportunities to maximize benefit and personalize therapy
A Growing Need...

1954:

1. The incidence of brain metastases is not less than 1 per cent and may be as high as 5 per cent of all cases of cancer. There are between 2000 and 10,000 patients in the United States each year with metastases to the brain.

2015:

“Because no national cancer registry documents brain metastases, the exact incidence is unknown, but it has been estimated that 98,000 to 170,000 new cases are diagnosed in the United States each year.” National Cancer Institute


2015 US Population : 320 million
Epidemiology

- Occurs in 4-15% of patients with solid tumors

- Autopsy studies suggest that this incidence may be higher

- Most commonly occurs in breast, lung, and melanoma patients
Risks

- Increased risk with prolonged disease course

- Higher propensity to develop leptomeningeal spread with history of brain metastases originating in the posterior fossa, and posterior fossa resection of metastases if piecemeal (vs en bloc resection)

- Risk following surgery may be histology dependent
CNS as the sanctuary site

- More than 99% of the brain’s capillaries are covered by a continuous endothelium: the blood brain barrier
- Compared with systemic endothelium, composed of very tight gap junctions: “zonulae occludentes”
- Lipid soluble, small molecules, can cross
- The following classes of systemic agents penetrate poorly:
  - Platinum salts: Carboplatin, Cisplatin
  - Anthracyclines: Doxorubicin, Daunorubicin, Epirubicin
  - Topoisomerases: Irinotecan, Etoposide
  - Vinca alkyloids: Vincristine, Vinblastine, Vinorelbine
  - Anti-metabolites: Cytarabine
Mechanisms of Spread

- Direct spread from dural based lesions
- Hematogenous spread via leptomeningeal veins and potentially the choroid plexus
- Venous spread of tumor cells originating from areas of marrow involvement
- Perineural spread along cranial or spinal nerves
Symptoms and Signs

- Headache, nausea or vomiting
- Posterior fossa signs
- Cranial nerve palsies
- Sensory and motor deficits
Investigations

- History and physical exam
- MRI Brain
- MRI Spine
- Lumbar puncture
MRI Brain
MRI Spine
Treatment Options

- Literature consists mainly of retrospective reviews with non-uniform treatment interventions.

- Radiation:
  - Whole brain
  - Craniospinal

- Chemotherapy: Intrathecal

- Best supportive care
Chemotherapy

- Most common agents include methotrexate, and liposomal cytarabine

- Among the largest series of patients with leptomeningeal disease, a prospective series of 137 patients suggested intrathecal methotrexate did not improve survival, however, a retrospective series of 103 patients did show mixed benefits

- Confers an increased risk for encephalopathy and myelopathy
Radiotherapy

- Across multiple studies, has been demonstrated to cause regression of symptoms, improve quality of life, and improve survival.

- Whole brain confers risk of neurocognitive deficits.

- Craniospinal treatment carries significant risk of myelosuppression, and with treatment delivered using photon therapy (most widespread approach), acute GI Toxicity (mucositis, esophagitis, enteritis) is expected.

- Craniospinal treatment delivered with proton therapy can significantly decrease dose beyond vertebral bodies, sparing the GI tract.
CSI: Photons
CSI: Protons

Penn Radiation Oncology

Penn Medicine
Prognosis

- Without treatment: measured in weeks
- With treatment: measured in months
- Median survival: 2-3 months; longest reported is 33.3 months
- Prognostic scoring: no formal grading system at present
Opportunities to improve management

- Epidemiology of LMD – collecting brain metastases and LMD incidence in registries

- Prognostic scoring to assist with patient selection for treatment

- Improving therapies: CSI delivered with protons

- Improving therapies: Targeted agents - histology matters: consider disease-specific scoring and treatment strategies
Example 1: NSCLC

- Up to 25% of patients have EGFR mutation positive NSCLC; 1/3 of these patients develop brain metastases
- Evidence that suggests intracranial metastases do not develop TKI-resistance similarly to systemic lesions
- Standard Erlotinib at 150 mg daily does not penetrate into the CNS well

"Pulsatile" high-dose weekly erlotinib for CNS metastases from *EGFR* mutant non-small cell lung cancer

Christian Grommes, Geoffrey R. Oxnard, Mark G. Kris, Vincent A. Miller, William Pao, Andrei I. Holodny, Jennifer L. Clarke, and Andrew B. Lassman
Prospective study of CSI for leptomeningeal disease

Use of proton therapy to limit toxicity in this population

Compare proton and photon plans created for each patient

Collection of toxicity, quality of life, and outcomes

Collect CTCs
One final thought...

"I'm afraid I'll fall and no one will hear me."
Surveillance and Secondary Prevention

- Lung NCCN Guidelines: No role for surveillance MRI Brain
- Breast NCCN Guidelines: Screening MRI only if recurrent or Stage IV disease
- Melanoma NCCN Guidelines: if sentinel LN+ “consider” MRI; if clinically LN+, “recommend” MRI
**Roadmap**

- **Epidemiology:** Global and disease specific
- **Site specific prognostic scoring and outcomes**
- **Combination with systemic agents:** where possible, molecular profiles of brain metastases lesions
- **Ongoing surveillance in high risk disease:** lung, locally advanced/metastatic breast; consider CTCs
- **Post-treatment support:** awareness of side effects, access to high grade imaging; neurocognitive support: medication, therapy
References

Acknowledgements

- Department of Radiation Oncology, CNS Division: Michelle Alonso-Basanta, Robert Lustig, Jay Dorsey

- Department of Neurosurgery

- James Janopaul-Naylor
Thank you