Neoplastic Meningitis: A Clear Indication For Intensive Hospice and Palliative Care

Richard Stephenson MD
Chief Medical Officer
Hospice & Palliative Care Center
Dick.Stephenson@hospicecarecenter.org
336.768.3972
Introduction

- My understanding has always been…
  - A rare but ominous development in cancer patients.
- But, 2 recent admissions to KBR and another to home care…
- Rare? What’s up?
- The KBR admissions were young women with Breast CA
  - Both very challenging for us
  - Both with very complex symptom management
  - Both with profound psychosocial & spiritual implications
Objectives

- Review definition, epidemiology, pathogenesis and diagnosis
- Understand prognostic variables
- Explore treatment options
- Anticipate the need for intensive symptom management
1\textsuperscript{st} Case at KBR

CH – 42 y/o WF presented to FMC with headache and neck rigidity, found leptomeningeal metastases (LM) as first site of recurrence < 1 year after original diagnosis

- Long and difficult course at FMC
- Transferred to KBR
  - Long and difficult course at KBR
  - Celebrated 43\textsuperscript{rd} birthday with us
- Relentless neurologic progression
  - Pain, numbness, paralysis
- 2 young children
- Ultimately, incrementally required sedation for comfort
2nd Case at KBR

JJ - 32 y/o AAF presented to FMC with HA, N/V and abdominal pain. Found to have liver metastases and in the hospital quickly developed cervical neck pain and persistent N/V and LM diagnosed.

Long and difficult course at FMC

Transferred to KBR

- Long and difficult course at KBR
- Celebrated 33rd birthday with us

Relentless neurologic progression

- Pain, HA, N/V, numbness, paralysis, blindness

2 young children

Ultimately, incrementally, required sedation for comfort
Terminology

- **Neoplastic meningitis**
  - the development of meningitis due to the infiltration of the subarachnoid space with cancer cells. Any kind of neoplasia, including leukemia and lymphoma

- **Carcinomatous meningitis**
  - Due to a carcinoma (solid tumors), doesn’t include leukemia and lymphoma

- **Leptomeningeal metastases (LM)**
  - Leptomeninges – arachnoid membrane and pia mater
  - Now seems to be the preferred term

- **Other terminology…**

- **Leptomeningeal carcinomatosis, meningeal carcinomatosis**
Pathogenesis

- Hematogenous dissemination to the meninges or
- Direct extension from para-meningeal or bony contiguous structures (bone, skull or vertebrae, regional lymph nodes or soft tissues) or
- Retrograde growth along spinal and/or cranial nerve roots
- Once in...
- Carried by bulk flow of CSF to basal cisterns and cauda equina where they settle 2⁰ gravity and slow flow
  - Which is why cranial and spinal nerve symptoms are so common
Incidence

● Seems to be happening more often!
  ■ Greater awareness of the condition by oncologists
    ● Higher index of suspicion & look for it
  ■ Improved diagnostic methods
  ■ Longer survival among patients with systemic malignancies...more time to develop
  ■ Larger molecule chemotherapies (that don’t cross Blood Brain Barrier)

● Occurs in ~ 5% of all cancers
  ■ 4 to 8% solid tumors; 5 to 15% leukemia and lymphomas (1000KBR 40%CA 5% LM = 50 pts/year?)
Melanoma and SCLC have strongest propensity for LM, up to 25%
Breast – 2 to 5% of all patients with metastatic breast CA
Based on frequency of each cancer
*Accept in Korea
  - Gastric

<table>
<thead>
<tr>
<th>Primary CA</th>
<th>% Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>27-50</td>
</tr>
<tr>
<td>Lung</td>
<td>22-36</td>
</tr>
<tr>
<td>AdenoCA</td>
<td>50-56</td>
</tr>
<tr>
<td>SqcellCA</td>
<td>26-36</td>
</tr>
<tr>
<td>SCLC</td>
<td>13-14</td>
</tr>
<tr>
<td>Melanoma</td>
<td>12</td>
</tr>
<tr>
<td>GU</td>
<td>5</td>
</tr>
<tr>
<td>Head &amp; N</td>
<td>2</td>
</tr>
<tr>
<td>Unkn 1⁰</td>
<td>2</td>
</tr>
</tbody>
</table>
Clinical Features

- Classically presents with pleomorphic findings in 3 domains of neurologic function
  - Cerebral (15-50%)
    - Headache and mental status changes
    - Followed by confusion, cognitive impairment, seizures, and hemiparesis
  - Cranial nerve dysfunction (35-50%)
    - Diploplia (VI, III, IV), trigeminal sensory or motor, cochlear dysfunction, and optic neuropathy
      - Cranial Nerve VI is most commonly involved? Why?
      - Name that Nerve!
  - Spinal (60-70%) –LEs > UEs
    - Weakness, dermatomal sensory loss, pain in the neck, back, or in radicular patterns
    - Classic nuchal rigidity only 15-20% (CH)
Symptoms* of (Breast) Meningeal Carcinomatosis from Gauthier et al

<table>
<thead>
<tr>
<th>Symptom</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>34%</td>
</tr>
<tr>
<td>Cranial nerve symptoms</td>
<td>25</td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>24</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>23</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>22</td>
</tr>
<tr>
<td>Radicular pain</td>
<td>21</td>
</tr>
<tr>
<td>Glasgow coma scale &lt; 15</td>
<td>21</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>19</td>
</tr>
<tr>
<td>Meningismis</td>
<td>12</td>
</tr>
<tr>
<td>Motor deficit</td>
<td>11</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>2</td>
</tr>
</tbody>
</table>

* Symptoms on presentation!
# Symptoms of (Gastric) Leptomeningeal Carcinomatosis

from Oh et al.

<table>
<thead>
<tr>
<th>Cerebral Symptoms</th>
<th>Cranial Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>85%</td>
</tr>
<tr>
<td>N &amp; V</td>
<td>59</td>
</tr>
<tr>
<td>Dizziness</td>
<td>24</td>
</tr>
<tr>
<td>Mental Change</td>
<td>22</td>
</tr>
<tr>
<td>Seizure</td>
<td>19</td>
</tr>
<tr>
<td>Gait</td>
<td>4</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>4</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2</td>
</tr>
<tr>
<td>Diploplia</td>
<td>6%</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>4</td>
</tr>
<tr>
<td>Facial palsy</td>
<td>2</td>
</tr>
<tr>
<td>Ptosis</td>
<td>2</td>
</tr>
<tr>
<td>Spinal Symptoms</td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>11</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>4</td>
</tr>
<tr>
<td>Back pain</td>
<td>2</td>
</tr>
</tbody>
</table>
Diagnosis

- Usually presents in patients with widespread disease – 70% (JJ)
  - May present after disease free interval – 20%
  - Sole site of relapsed DZ with increasing frequency (CH)
  - Occasionally in absence of systemic DZ – 5%
- Symptoms sometimes for weeks or months (JJ&CH)
- May seem benign or stable (CH was being treated for migraine and JJ for vertigo 2º viral illness)
- Once recognized often progresses rapidly
- High index of suspicion with multifocal Neurologic dysfunction
Diagnostic Testing

- Gadolinium enhanced MRI
  - If Lumbar Puncture is done first may cause false (+) MRI
  - Neither CH or JJ could have MRI because of metal in expandable breast implants

- Examination of CSF
  - Cytology maybe false (-) ~ 10-30%
  - Clinical suspicion, + MRI, and CSF signs but negative cytology may be enough for Dx and Rx

- CSF flow study
  - Neither of our patients had this, rarely done locally?

- Meningeal biopsy
<table>
<thead>
<tr>
<th>TEST</th>
<th>MEASUREMENT</th>
<th>POSITIVE FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar puncture</td>
<td>Lymphocytic pleocytosis</td>
<td>&gt;70%</td>
</tr>
<tr>
<td></td>
<td>Elevated opening pressure</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Elevated protein</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>Reduced glucose</td>
<td>30%-40%</td>
</tr>
<tr>
<td></td>
<td>Cytology after 1 lumbar puncture</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Cytology after 3 lumbar punctures</td>
<td>90% (&lt; 100%)</td>
</tr>
<tr>
<td></td>
<td>CSF markers</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>Immunohistochemistry</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>PCR</td>
<td>Variable</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>Meningeal enhancement</td>
<td>&gt;50%</td>
</tr>
<tr>
<td></td>
<td>Enlarged ventricles</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>Spine MRI/myelogram</td>
<td>Subarachnoid masses</td>
<td>&lt;25%</td>
</tr>
<tr>
<td></td>
<td>Meningeal enhancement</td>
<td>&gt;50%</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

From Bradley: Neurology in Clinical Practice, 5th ed.
<table>
<thead>
<tr>
<th>NEOPLASTIC</th>
<th>From Bradley: Neurology in Clinical Practice, 5th ed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal metastases</td>
<td></td>
</tr>
<tr>
<td>Dural metastases</td>
<td></td>
</tr>
<tr>
<td>Castleman's disease*</td>
<td></td>
</tr>
<tr>
<td>INFECTIONS</td>
<td></td>
</tr>
<tr>
<td>Bacterial/viral meningitis</td>
<td></td>
</tr>
<tr>
<td>Fungal infections, including cryptococcus</td>
<td></td>
</tr>
<tr>
<td>Lyme disease</td>
<td></td>
</tr>
<tr>
<td>Neurocysticercosis</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
</tr>
<tr>
<td>GRANULOMATOUS DISORDERS</td>
<td></td>
</tr>
<tr>
<td>Histiocytosis</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td>Wegener's granulomatosis</td>
<td></td>
</tr>
<tr>
<td>INFLAMMATORY DISORDERS</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic encephalomyelitis</td>
<td></td>
</tr>
<tr>
<td>Relapsing polychondritis</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid nodules</td>
<td></td>
</tr>
<tr>
<td>Vasculitis (including granulomatous angiitis)</td>
<td></td>
</tr>
</tbody>
</table>

* “benign”CNS lymphoma associated with HIV
Prognosis of LM

- Bad…ominous…grave…terminal
- Median survival untreated patients is 4-6 weeks
  - Death from progression of neurologic dysfunction
- Treatment is intended to improve or stabilize neurologic status, maintain neurologic QOL, and prolong survival
- Fixed neurologic deficits rarely improve, but progression may be halted in some patients, and median survival can be increased to 4-6 months
  - Only pain-related Nx Sx improve; confusion, Cr Ns, ataxia, weakness minimally improve or stabilize
- Breast CA (of solid tumors) responds best
  - MLOS:Survival 6 mos; 11-25% 1 year survival
- Who to treat?
Bad Prognostic Signs (bad to worst)

- Generally accepted that patients do poorly with:
  - Poor performance status
  - Multiple fixed neurologic deficits
  - Bulky CNS disease (1/3 of patients)
  - Coexistent carcinomatous encephalopathy
  - CSF flow abnormalities (1/3 of patients)
  - Widely metastatic aggressive cancers
    - 75% have progressive systemic cancer
KPS is easy to determine

How about in patients matched for all the other bad prognostic signs?

KPS < 70 vs. KPS > 70 matched for:

- Age, 1° tumor site, site of NM (Cr Ns or cord), treatment (RT and chemo; systemic and intraventricular), CSF compartmentalization, encephalopathy, and bulky CNS disease
## Karnofsky Score

<table>
<thead>
<tr>
<th>Karnofsky Score (KS)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>
Survival in patients with neoplastic meningitis by Karnofsky performance status (KPS) score

Conclusions

- A low Karnofsky performance score predicts poor survival in patients with NM.

- Patients with low Karnofsky performance score may best be served by offering supportive care.

- Both CH and JJ were, “on the cusp” at 60-70%.
Survival of Breast Cancer Patients With Meningeal Carcinomatosis  

- Most common cause of nonhematologic MC
- Review of 91 Breast CA patients 2000-2007
- Report clinical and biologic features
- Determine significant prognostic features for response to therapy
- Develop and propose a prognostic score
Results

- Multivariate statistical analysis of prognostic features
- 4 features associated with poor survival
  1. Poor performance status (ECOG 3-4)
  2. Number of prior chemotherapy regimens (>3)
  3. Negative hormone receptor status
  4. High Cyfra 21-1 levels (Br Ca tumor marker)
## ECOG PERFORMANCE STATUS SCALE

<table>
<thead>
<tr>
<th>ECOG (Zubrod)</th>
<th>Karnofsky</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>1</td>
<td>80-90</td>
<td>Symptomatic, fully ambulatory</td>
</tr>
<tr>
<td>2</td>
<td>60-70</td>
<td>Symptomatic, in bed less than 50% of the day</td>
</tr>
<tr>
<td>3</td>
<td>40-50</td>
<td>Symptomatic, in bed more than 50% of the day, but not bedridden</td>
</tr>
<tr>
<td>4</td>
<td>20-30</td>
<td>Bedridden</td>
</tr>
</tbody>
</table>
(A–C) Overall survival (OS) and prognostic scores.

B. ECOG 3-4 = 1  
HR(+) = 0; (-) = 1  
CT>3 lines = 1  
Cyfra high = 1

C. Eliminated Cyfra  
(not widely done)

Both CH and JJ  
Score = 2 and died  
at ~ 12 weeks.

Treatment

- Despite 3 decades of effort
- Treatment options remain limited
  1. Need to treat entire neuraxis
  2. Close proximity of tumor to neural structures
  3. Limit RT and CT because of neurotoxicity
  4. Blood-CSF Barrier
  5. Intrinsic resistance of solid tumors
  6. Routine presence of other sites of metastatic disease
- 1/3 opt out; 1/3 too sick; 1/3 treated
Treatment Overview

- **Surgery**
  - Occasional meningeal Bx for Dx
  - Placement of intraventricular (Ommaya) reservoir for CSF access
  - CSF diversionary procedures (V-P shunt)

- **Radiation**
  - Focused
  - Whole brain
  - Spinal

- **Chemotherapy**
  - Intrathecal
  - Systemic
Treatment Complications

- Ommaya reservoir
  - 1% hemorrhage; 5% infection
- Impaired CSF flow due to obstruction
  - Chemo may cause seizures, arachnoiditis (N/V and MS changes)
- Aseptic meningitis
- Necrotizing leukoencephalopathy
  - Most common with IT Mtx following RT
  - Progressive dementia, debility and death
- Transverse myelitis
  - IT Chemo + RT cord
# Table 56F-6 -- Treatment of Leptomeningeal Metastases

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation therapy to sites of symptomatic and bulky disease</td>
</tr>
<tr>
<td>Methotrexate (10 mg twice weekly) + leucovorin</td>
</tr>
<tr>
<td>Thiotepa (10 mg twice weekly)</td>
</tr>
<tr>
<td>Cytarabine (50 mg twice weekly)</td>
</tr>
<tr>
<td>Cytarabine (DepoCyt) (50 mg every 2 weeks)</td>
</tr>
<tr>
<td>Systemic chemotherapy (e.g., high-dose methotrexate)</td>
</tr>
<tr>
<td>Optimal treatment of systemic disease</td>
</tr>
</tbody>
</table>

From Bradley: Neurology in Clinical Practice, 5th ed.
Figure 1. Treatment algorithm of neoplastic meningitis
Ommaya Reservoir

Vs. LP

- Repeated access
- Better tolerated
  - But a procedure
- LP admin 10% leak
- Improved drug distribution
- Side port to convert to shunt if necessary
Experimental Therapies

- New chemotherapeutic agents
- Intrathecal biologic agents, antibodies, and immunoconjugates
- Radioisotopes and radioimmunoconjugates
- Intensive systemic chemotherapy
  - High-dose Mtx with rescue
- Gene therapy
Intensive Hospice & Palliative Care

- All treatments are palliative!
- No patients are cured of LM!
- All will die! Some of progressive systemic disease but most with progressive neurologic dysfunction with many if not most of the symptoms noted earlier!
- Patients appropriate for aggressive treatment also need aggressive Sx Rx and comprehensive, holistic PC
- All others should get intensive H & PC
- What does that mean?
  - There is no literature to tell us what to expect and what to do RE SxRx and best supportive care
  - H/O and PC texts
  - H/O or PC journals
- Let’s write that article!
## Symptoms in Patients Dying of (Breast) Meningeal Carcinomatosis

Services MS et al. *J Impt Stuff* 2010

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>34%</td>
<td>100%</td>
</tr>
<tr>
<td>Cranial nerve symptoms</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>23</td>
<td>100</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>22</td>
<td>100</td>
</tr>
<tr>
<td>Radicular pain</td>
<td>21</td>
<td>100</td>
</tr>
<tr>
<td>Glasgow coma scale &lt; 15</td>
<td>21</td>
<td>100</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>19</td>
<td>100</td>
</tr>
<tr>
<td>Meningismis</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>Motor deficit</td>
<td>11</td>
<td>100</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

(from Gauthier et al)
Challenges in Intensive Symptom Management of Leptomeningeal Metastases Services MS et al. J Impt Stuff 2010

- Reporting on our recent series of patients (n=2)
  - We can find more patients (PHO/FMC record review?)
- Severe Headache
  - Steroids, opioids, and complementary therapies
- Radicular pain
  - Steroids, opioids (methadone), gabapentin (or other anticonvulsants (keppra?), ketamine, muscle relaxants (benzos and baclofen))
  - Complementary therapies (PT, massage, guided imagery)
- Nausea & Vomiting
  - Steroids, anticholinergics (cochlear involvement), target every receptor if refractory (haloperidol, ondansetron, antihistamines, anticholinergics, cannabinoids)
Refactory Pain

- Opioid dosing
- Opioid rotation
  - Fentanyl and methadone
- Maximal adjuvant therapy (neuropathic)
  - Anticonvulsants, antidepresents
  - Ketorolac (Toradol)
  - Ketamine
- Psychosocial and spiritual therapies
- Total sedation
Use That Ommaya?

Intraventricular Administration of Morphine for Control of Intractable Cancer Pain in 90 Patients. Karavelis et al


No recent literature

“We haven’t done that in years.” R Rauck
Once Daily Administration of Morphine

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57</td>
<td>58</td>
<td>23</td>
<td>80</td>
</tr>
<tr>
<td>Pain duration (mo)</td>
<td>10</td>
<td>6</td>
<td>0.5</td>
<td>120</td>
</tr>
<tr>
<td>Duration of reservoir use (d)</td>
<td>95</td>
<td>46</td>
<td>1</td>
<td>1362</td>
</tr>
<tr>
<td>Morphine dose (mg)</td>
<td>1</td>
<td>1</td>
<td>0.25</td>
<td>4</td>
</tr>
<tr>
<td>Quality of analgesia (%)</td>
<td>78</td>
<td>90</td>
<td>0^a</td>
<td>100</td>
</tr>
<tr>
<td>Duration of analgesia (h)</td>
<td>22</td>
<td>24</td>
<td>0^a</td>
<td>72</td>
</tr>
</tbody>
</table>

^a Complications.

Theoretically – does it make sense to consider intraventricular administration of other medications using Ommaya reservoir already in place? Need a consultant!
Seizures –
- Keppra, phenytoin, steroids, benzos, midazolam

Constipation – paresis + opioids
- Broad spectrum oral agents, MNTX, disimpaction

Psychosis – hallucinations, delusions, paranoia
- Haldol, Thorazine, minimize steroids

Paresis, paresthesia, paralysis – I
- Intensive personal care
- Bed, mattress

Senses - visual (to blind), auditory (to deaf)
- CH could no longer read; JJ could no longer see

Anxiety
- Long-acting benzos, companionship

Physical space
- Bed, Mattress
- Quiet, dark/light, room for PCG(s)
Depression
- Ritalin, Remeron, Effexor
- Complementary, counseling, pastoral care

Social
- Institutionalized for Sx Rx and personal care needs
- Loss of roles
- Counseling, pastoral care, social support

Spiritual
- Fatal + suffering
- Losses
- Profound existential suffering

JJ - “Why am I still here?!?”
“I thought I’d wake up dead and in heaven!”
“Let me go! Don’t be selfish, let me go!”

Incremental, palliative sedation
Great Teachers

- CH and JJ
- Medical students
- WE ALL learned so much
- Paybacks…
- A devastating complication with an ominous prognosis and high likelihood of intensive symptom management
- We can do a better job
Comments & Questions
Selected References