Primary Central Nervous System Lymphoma

Lymphoma Tumor Board

May 19, 2017
Figure 1
Respective yearly incidence of the different primary brain tumour types in adults aged 65–74 years between 1998 and 2002. This distribution is representative of the distribution of primary brain tumours in adults aged 20–84 years. Data taken from the Central Brain Tumor Registry of the United States.²
Primary CNS Lymphoma (PCNSL)

- Aggressive malignancy that arises exclusively in the CNS
- Represents 4% of intracranial neoplasms and 4-6% of all extranodal lymphomas
- Represents around 20% of all cases of lymphoma in HIV-infected individuals
- Highly associated with EBV in immunodeficient patients
- Patients present with impaired general condition and poor performance status more often than other lymphomas
- Typically appears in 50-60 yr. olds
- Spinal cord lymphoma is the rarest manifestation of PCNSL
  - Often arises in the upper thoracic and lower cervical regions of the spinal cord
- Patients present with seizure, headache, cranial nerve findings, altered mental status, or other focal neurological deficits
- Symptoms at presentation may also include:
  - Fever
  - Night sweats
  - Weight loss
  - Diplopia
  - Dysphagia
  - Vertigo
  - Monocular vision loss
Diagnosis

- Brain biopsy
- MRI or contrast CT scan will show ring-enhancing lesions in the deep white matter
- 95% of cases will demonstrate homogenous enhancement localized to the tumor, with rare necrosis
  - This characteristic is useful in distinguishing PCNSL from glioblastoma
- Major differential diagnosis is cerebral toxoplasmosis
  - This is prevalent in AIDS patients and also presents with ring-enhanced lesions
- Lesions are solitary in 65% of patients and multifocal in 35%
- Cerebral hemisphere disease is most common (38%), followed by lesions within the thalamus/basal ganglia (16%), corpus callosum (14%), ventricular region (12%), and cerebellum (9%) (representative MR images below)
Diagnostic evaluation of suspected PCNSL

Clinical Presentation

MRI, CSF & Eye Exam

Diagnostic Procedure: Bx, Resection, Cytology or Flow-Cytometry

Decadron 4 mg q6h
planned taper over 2-3 wks

Staging: MRI, CSF, Eye BM Bx, CT C/A/P,
 +/- PET, +/- testes U/S

LFT’s, LDH, Lytes, CrCl
Hep B, C, HIV,
PCP & HSV Prophylaxis

PCNSL

Indolent Histology

Aggressive Histology

Rituximab, Fludarabine,
 +/- Involved-field XRT
(HD-MTX for CLL/SLL)

HD-MTX Candidate ?

Yes

MT-R Induction

No

Temozolomide +/- Rituximab

PD  

CR, PR, SD

MT-R Induction

ASCT, WBRT or Clinical Trial

Consider EA Consolidation

Magnetic resonance imaging of PCNSL

A

B

C

D

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Intraocular lymphoma – a rare subtype of PCNSL


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Pathologic features of PCNSL

A

B

C

D

Classic histopathologic picture of PCNSL with diffuse large B-cell lymphoma morphology

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Somatic mutations and patterns of genetic alterations in PCNSL and PTL (primary testicular lymphoma)

Chromosomal rearrangements in PCNSL and PTL

PCNSLs, PTLs, and PMBLs clustered by recurrent CNAs

Unique combinations of structural alterations in discrete large B-cell lymphoma subtypes

<table>
<thead>
<tr>
<th>Genomic instability</th>
<th>DLBCL</th>
<th>PTL</th>
<th>EBV* PCNSL</th>
<th>PMBL</th>
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<tbody>
<tr>
<td><strong>CDKN2A</strong>&lt;sup&gt;loss&lt;/sup&gt; bi-alleic</td>
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<tr>
<td>CNAs of additional p53/cell cycle components</td>
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<td></td>
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<tr>
<td>Total CNAs</td>
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### Oncogenic TLR and BCR Signaling

<table>
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<th>Genes</th>
<th>DLBCL</th>
<th>PTL</th>
<th>EBV* PCNSL</th>
<th>PMBL</th>
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<tbody>
<tr>
<td><strong>MYD88</strong>&lt;sup&gt;L265P&lt;/sup&gt;</td>
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<tr>
<td><strong>NFKBIZ</strong>&lt;sup&gt;gain&lt;/sup&gt;</td>
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<tr>
<td><strong>NFKBIZ</strong>&lt;sup&gt;gain&lt;/sup&gt; and/or <strong>MYD88</strong>&lt;sup&gt;L265P&lt;/sup&gt;</td>
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<td><strong>CD79B</strong>&lt;sup&gt;Y196mut&lt;/sup&gt;</td>
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### PD-1 Ligand Deregulation

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<th>EBV* PCNSL</th>
<th>PMBL</th>
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<tr>
<td><strong>PD-L1</strong> or <strong>PDL-2</strong> translocation</td>
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Treatment of PCNSL

- Surgical resection is usually ineffective because of the depth of the tumor
- Irradiation and corticosteroids can produce partial response
- Tumor recurs in more than 90% of patients
- Median survival is 10-18 months
- IV methotrexate (MTX) and folinic acid (leucovorin) may extend survival
- Radiation is not recommended to be used with methotrexate because of increased risk of leukoencephalopathy and dementia in older patients
- Standard CHOP therapies are ineffective in PCNSL due to poor penetration of the agents through the blood-brain barrier (BBB)
- Antimetabolites such as MTX and cytarabine (ara-C) – which cross BBB after IV administration – constitute the backbone of most anti-PCNSL regimens, with proven efficacy in prospective trials
Flow chart of management of PCNSL from presentation to therapeutic decision in ordinary clinical practice

**Presenting symptoms**
- focal deficits (70%),
- neuropsychiatric sym. (43%),
- high intracranial pressure (33%),
- seizures (14%),
- headache, ocular symptoms, confusion, and lethargy.

**Sites of disease**
- Brain hemispheres (38%),
- thalamus/basal ganglia (16%),
- corpus callosum (14%),
- periventricular region (12%),
- cerebellum (9%),
- eyes (5-20%),
- meninges (18%),
- spinal cord (1%),
- cranial and spinal nerves (<1%).

**Neuroimaging (MRI)**
- Lesions are hypointense in T1, isointense to hypointense on T2,
- reduced ADC,
- variable surrounding edema,
- strong enhancement.

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**PCNSL suspicion**

**Stereotactic biopsy**

**Diffuse large B-cell lymphoma**

**Staging**
- Physical examination,
- routine blood studies,
- Whole-brain MRI,
- Contrast total body CT scan,
- Ophthalmologic evaluation,
- CSF examination,
- Bone marrow biopsy,
- Testicular ultrasonography,
- 18FDG-PET (investigational).

**Baseline evaluations**
- Neurological examination,
- Biochemical serum profile,
- Neuropsychiatric tests,
- Renal functionality tests,
- Hepatic functionality tests,
- Cardiac functionality tests,
- HIV, Hepatitis B & C virus.

**Prognostic factors**
- Age (<60 vs. >60 yrs.),
- Performance status (0-1 vs. ≥2),
- LDH (normal vs. elevated),
- CSF protein (normal vs. elevated),
- Deep regions (no vs. yes).

**Exclusion of systemic disease.**
- Extension: eyes, CSF, etc.

**Treatment feasibility.**

**Risk**

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**Therapeutic decision**

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Flow chart of therapeutic management of PCNSL in everyday practice

Lymphoma histotype – Stage IE

Indolent lymphoma¹

Local treatment

Indolent lymphoma¹

DLBCL

Age – Comorbidity – Prognostic score

Young and fit patient

HD-MTX + HD-ara-C combination²

CR - PR - SD

Individualized treatment³

WBRT⁷

HDC/ASCT

Elderly patient (> 70 yrs.)

HD-MTX-based chemotherapy⁴

PD

WBRT 40-45 Gy

Unfit (chemo contraindicated)

R-CHOP + HD-MTX ± ara-C

CR

PR - SD

Individualized treatment⁶

WBRT⁷

Wait & watch

Unfit (chemo contraindicated)

WBRT 40-50 Gy ± steroid maintenance

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# Salvage treatment for PCNSL

<table>
<thead>
<tr>
<th>Treatment, Ref.</th>
<th>Study</th>
<th>No.</th>
<th>Median age, y</th>
<th>Prior RT, %</th>
<th>CR + PR, %</th>
<th>PFS</th>
<th>OS</th>
<th>1–y OS, %</th>
<th>Grade 3–4 neutropenia, %</th>
<th>Grade 3–4 thrombocytopenia, %</th>
<th>Other toxicities, %</th>
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<tbody>
<tr>
<td>VP16 + Ifosfamide + Ara-C⁹⁷</td>
<td>R</td>
<td>16</td>
<td>54</td>
<td>100</td>
<td>37 + 0</td>
<td>4.5</td>
<td>6.0</td>
<td>41</td>
<td>69</td>
<td>50</td>
<td>37</td>
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<tr>
<td>i. a. Carboplatin ± VP16 ± CTX ± RT⁹⁸</td>
<td>R</td>
<td>37</td>
<td>57</td>
<td>24</td>
<td>24 + 11</td>
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<td>6.8</td>
<td>25</td>
<td>22</td>
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<td>22</td>
<td>58</td>
<td>14</td>
<td>73 + 19</td>
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<td>70</td>
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<tr>
<td>Temozolomide + rituximab⁹⁹</td>
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<td>15</td>
<td>69</td>
<td>13</td>
<td>40 + 13</td>
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<td>10.5</td>
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<tr>
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<td>NR</td>
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<td>19.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>58†</td>
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Progress in the treatment of PCNSL


A  B  C

0  0.5  1  1.5  2  2.5  3  3.5  4  4.5  5

Year

100  75  50  25  0

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Long-term outcome in PCNSL patients treated with high-dose methotrexate and deferred radiation

Figure 1.
Kaplan-Meier curves for overall survival (Overall), disease specific survival (DSS), and progression free survival (PFS) for the 25 patients treated with high dose methotrexate.
References

- https://en.wikipedia.org/wiki/Primary_central_nervous_system_lymphoma