Management of Primary CNS Lymphomas

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PCNSL - Talk Tour

- Definition
- Epidemiology
- Aetiopathogenesis and pathology
- Presentation
- Diagnostic evaluation
- Prognostication
- Treatment
  - Role of Radiotherapy
  - Combined modality approach
  - Role of Chemotherapy
  - Role of Surgery
  - Role of High dose chemotherapy and SCT
- Management of primary Intra-ocular Lymphoma
Definitions – PCNSL

**Primary central nervous system lymphoma (PCNSL)** is a NHL confined to the cranio-spinal axis (brain, leptomeninges, spinal cord or eyes) **without** evidence of systemic spread.

**Primary Intra-ocular lymphoma (PIOL)** –
PCNSL primarily involving the eye initially

NHL sometimes spares the brain entirely and involves cranial nerves, nerve roots, or cauda equina owing to primary infiltration of the leptomeninges. On rare occasions there may be predominant infiltration of nerve roots, nerve plexus, or peripheral nerves only - a condition referred to as **Neurolymphomatosis (NL)**.
PCNSL - Epidemiology

- PCNSL is rare.
- Less than 5% of primary brain tumors (2.7% of all primary brain tumors diagnosed in the US from 1995 to 1999).
- Risk is more in patients who have congenital or AIDS, (3600 times risk) including organ transplant recipients.
- Diagnosed in at least 2% of HIV-infected individuals.
- Is an AIDS-defining illness.
- Incidence has decreased with availability of HAART.
Aetiopathogenesis

Role of Epstein-Barr virus (EBV) genome

Detected in 0% to 20% of PCNSLs patients who do not have immunocompromise.

Nearly 100% in AIDS PCNSL

Latent membrane protein-1 IHC is positive in AIDS PCNSL compared with AIDS-related systemic non-Hodgkin’s lymphomas suggesting a potentially different pathogenesis.
90% are DLBCL

10% are poorly characterized low-grade lymphomas, Burkitt’s lymphomas, and T-cell lymphomas.

The DLBCL type of PCNSL is composed of immunoblasts or centroblasts

Have a predilection for blood vessels, resulting in lymphoid clustering around small cerebral vessels

PCNSL is a late germinal center or post-germinal center lymphoid neoplasm.

The tumor arises in an Extraneural environment with subsequent localization to the CNS, possibly by virtue of a specific Neurotropism.
Presentation - PCNSL

Typically present with neurologic symptoms and signs rather than systemic “B” symptoms

PCNSL involving the leptomeninges show no clinical signs of leptomeningeal disease usually (only 16-41%).

Approximately 20% of patients will have ocular involvement at the time of PCNSL diagnosis. Both eyes affected in most patients.

Patients with intraocular lymphoma generally complain of floaters, blurred vision, diminished visual acuity, and painful red eyes.
Diagnostic evaluation

Clinical Evaluation
Imaging
Pathology
Laboratory evaluation
### Diagnostic Evaluation

**International PCNSL Collaborative group Guidelines for baseline evaluation**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Clinical</th>
<th>Laboratory</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central review of Pathology</td>
<td>Complete medical and neurological examination</td>
<td>HIV Serology</td>
<td>Contrast enhanced cranial MRI</td>
</tr>
<tr>
<td>Dilated eye examination including slit lamp examination</td>
<td>CSF cytology, Flow cytometry IgH PCR</td>
<td></td>
<td>CT scan – Chest, abdomen and Pelvis</td>
</tr>
<tr>
<td>Immuno-phenotyping</td>
<td>Record prognostic factors (Age, PS)</td>
<td>24 hour urine collection for Creatinine clearance</td>
<td>Bone marrow aspiration and Biopsy</td>
</tr>
<tr>
<td>Serial evaluation of cognitive function</td>
<td></td>
<td></td>
<td>Testicular USG in elderly</td>
</tr>
</tbody>
</table>

Contrast-enhanced cranial MRI is the optimal imaging modality for assessing patients with PCNSL unless contra-indicated.

PCNSL is often isodense to hyperdense on CT images and isointense to hypointense on T2-weighted MRI images, a finding that is attributed to its high cell density and scant cytoplasm.

Post-contrast CT or MR images, typically reveal a homogeneous pattern of enhancement.

Enhancement along the Virchow-Robin spaces, although not constant, is a highly specific feature.
Neuro-imaging in PCNSL
Pattern of involvement

Prognostication- PCNSL

Ann Arbor Staging does not apply in PCNSL

International Extranodal Lymphoma Study Group –
Parameters associated with poor prognosis:

- Age older than 60 years (most powerful prognostic factor)
- ECOG performance status greater than 1
- Elevated serum LDH
- High CSF protein concentration
- Tumor location within the deep regions of the brain (periventricular regions, basal ganglia, brainstem, and/or cerebellum).

Biochemical markers –

BCL-6 over-expression – associated with longer survival (101 months versus 14.7 months in those in whom it is not expressed)

P53 and c-Myc expression associated with worse prognosis
Prognostication-PCNSL

- Age older than 60 years
- ECOG PS greater than 1
- Elevated serum LDH
- High CSF protein conc
- Tumor location within the deep regions of brain

<table>
<thead>
<tr>
<th>Score</th>
<th>OS at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or 1</td>
<td>80%</td>
</tr>
<tr>
<td>2 or 3</td>
<td>48%</td>
</tr>
<tr>
<td>4 or 5</td>
<td>15%</td>
</tr>
</tbody>
</table>

PCNSL – Treatment aspects

- Extremely radiosensitive and chemo-sensitive tumor
- Relapses are common
- Current trials seek to identify the most appropriate combined modality treatment
- Minimizing the permanent treatment induced neurological deficits is a significant consideration in treating PCNSL
Role of steroids in the management of PCNSL

- **Exert apoptotic effect** on lymphoid cells through cytoplasmic steroid receptors.

- Dexamethasone has been associated with initial CR (15%) and PR (25%)

- **Remission is only temporary** although it can outlast the steroid administration.

- **Resistance** is common on re-exposure.

- **Should be avoided during evaluation of patient** and before biopsy and CSF examination – False negative results

- May be started after Bx is done to control vasogenic edema and resultant mass effect.

- Unclear whether steroids need to be an integral part of any regimen as is true for systemic lymphomas
Radiotherapy alone in PCNSL

- PCNSL – **Multifocal** in brain
- Historically RT involves whole brain RT
- RT in PCNSL does not achieve comparable disease control or overall survival as compared to systemic NHL (IE disease)
- 5 year survival is 4%

<table>
<thead>
<tr>
<th>Dose</th>
<th>36 to 40Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>90%</td>
</tr>
<tr>
<td>Median OS</td>
<td>11.6 mo</td>
</tr>
<tr>
<td>Relapses within irradiated field</td>
<td>61%</td>
</tr>
</tbody>
</table>

**Increasing dose to 60Gy does not decrease local relapses**

**Increased likelihood of treatment related neurotoxicity especially in patients above 60 years**

Reasons for failure of RT as a single modality of treatment in PCNSL

✓ PCNSL may be confined to the nervous system but it is potentially disseminated within it at diagnosis.

✓ Ocular or CSF involvement may be present, even if not identified on a staging evaluation. These areas could be potential reservoirs of untreated disease if the patient receives only WBRT.

✓ PCNSL may have a unique biology that accounts for its worse outcome despite its comparable histological appearance to most systemic diffuse large B-cell lymphoma,
Chemotherapy in PCNSL

Standard use of systemic NHL treatment regimens in PCNSL –

• Associated with transient responses of brain lesions,
• Frequent recurrences
• Florid leptomeningeal involvement at relapse.

Four prospective trials (one randomized)

All failed to show an advantage of CHOP/CHOD plus WBRT over WBRT alone.

CHOP has no role in the treatment of PCNSL
Chemotherapy in PCNSL
The role of Methotrexate

- First recognized when it was discovered that patients who had systemic NHL that relapsed in the CNS responded to high-dose MTX.

- The ability of high-dose MTX to penetrate the CNS makes it an attractive agent for the treatment of PCNSL.

- Rapid infusion of high-dose MTX over three hours greatly raises the drug level in the CSF (maximum therapeutic concentration in 4-6 hours after the start of an infusion), and remains above the minimum therapeutic concentration in the CSF for up to 24 hours (blood to CSF ratio of 30:1).

- Methotrexate (MTX)-based regimens are the only regimens with a significant advantage over RT alone.
Chemotherapy in PCNSL
The role of Methotrexate

Cytotoxic CSF levels of methotrexate achieved is sufficient to treat microscopic or macroscopic tumor in the leptomeninges is avoided in most PCNSL patients.

Commonly used methotrexate-based, combined-modality regimen consists of five cycles (10 weeks) of pre-irradiation

- IV MTX 2.5 g/m2
- IV Vincristine 1.4 mg/m2
- Oral Procarbazine 100 mg/m2/d for 7 days,
- IT Methotrexate 12 mg,
- Dexamethasone taper

Followed by WBRT 45 Gy and post-WBRT high-dose Cytarabine 3 g/m2/d for two doses.
# Chemotherapy in PCNSL

## The role of Chemotherapy Plus WBRT - Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of pts</th>
<th>Regimen</th>
<th>Radiotherapy (Gy)</th>
<th>RR (%)</th>
<th>OS (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabbai et al, 1989</td>
<td>13</td>
<td>IV MTX (3.5 g/m²)</td>
<td>30–44</td>
<td>92</td>
<td>9.5</td>
</tr>
<tr>
<td>DeAngelis et al, 1992</td>
<td>31</td>
<td>IV MTX (1 g/m²) + IT MTX (12 mg × 6) IV MTX (3.5 g/m²)</td>
<td>40 + 4.4 boost</td>
<td>64</td>
<td>41</td>
</tr>
<tr>
<td>Glass et al, 1994</td>
<td>25</td>
<td>MPV(IV MTX 3.5 g/m²) + IV ara-C + IT MTX (12 mg × 3)</td>
<td>30–44</td>
<td>88</td>
<td>33</td>
</tr>
<tr>
<td>Abrey et al, 2000</td>
<td>52</td>
<td>MPV (IV MTX 3 g/m²) MPV (IV MTX 2.5 g/m²) + IT MTX (12 mg × 5)</td>
<td>45 in 35/52 pts</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>Ferreri et al, 2001</td>
<td>13</td>
<td>MBVP (IV MTX 3 g/m²) + IT</td>
<td>39.6</td>
<td>92</td>
<td>25+</td>
</tr>
<tr>
<td>DeAngelis et al, 2002</td>
<td>102</td>
<td>MTX (15 mg) +</td>
<td>45</td>
<td>94</td>
<td>30+</td>
</tr>
<tr>
<td>Poortmans et al, 2003</td>
<td>52</td>
<td>IT ara-C (40 mg) + hydrocortisone (25 mg × 2)</td>
<td>30 + 10 boost</td>
<td>81</td>
<td>46</td>
</tr>
</tbody>
</table>

### Chemotherapy in PCNSL

#### The role of Chemotherapy alone - Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>pts</th>
<th>Regimen</th>
<th>RR (%)</th>
<th>OS (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freilich et al, 1996</td>
<td>13</td>
<td>IV MTX (1 g/m2 or 3.5 g/m2) + IT MTX (12 mg) + VCR (1.4 mg/m2) + PO procarbazine (100 mg/m2) + IV ara-C (3 g/m2); 5 pts with IV thiotepa (40 mg) in place of VCR</td>
<td>92</td>
<td>30.5</td>
</tr>
<tr>
<td>Cheng et al 1998</td>
<td>19</td>
<td>BOMES IV Mtx (8gms/m2) plus IT Mtx (12mg/m2 x 4 if positive CSF)</td>
<td>84</td>
<td>6 PFS</td>
</tr>
<tr>
<td>Sandor et al 1998</td>
<td>14</td>
<td>MTV (IV Mtx 8gms/m2 plus IT Arac (15mg/day x 3 days x2doses)</td>
<td>100</td>
<td>16.5 PFS</td>
</tr>
<tr>
<td>Guha</td>
<td>31</td>
<td>IV MTX (8 g/m2) + consolidation with 3.5 g/m2 every 3rd month</td>
<td>100</td>
<td>30+</td>
</tr>
<tr>
<td>McAllister et al, 2000</td>
<td>74</td>
<td>IA MTX (2.5 g) + CTX + etoposide</td>
<td>65</td>
<td>40.7</td>
</tr>
<tr>
<td>Batchelor et al, 2003</td>
<td>25</td>
<td>25 IV MTX (8 g/m2)</td>
<td>74</td>
<td>22.8+</td>
</tr>
<tr>
<td>Pels et al, 2003</td>
<td>65</td>
<td>IV MTX (5 g/m2) + IV ara-C (3 g/m2) + ifosfamide/vincristine/cyclophosphamide/dexamethasone + IT MTX (3 mg) + IT ara-C30 mg) + prednisone (2.5 mg × 3)</td>
<td>71</td>
<td></td>
</tr>
</tbody>
</table>

Chemotherapy alone in PCNSL

Current status

Considered in PCNSL patients older than age 60 a group at highest risk for radiation-related neurotoxicity.

Durable responses are possible, although most patients eventually experience relapse.

<table>
<thead>
<tr>
<th>One multicenter phase II study –</th>
<th>Multi-agent CT without RT – 65 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-agent therapy with high-dose Mtx 8 g/m2</td>
<td>ORR -71%</td>
</tr>
<tr>
<td>CR rate of 52%, PFS of 12.8 months, OS of 55.4 months, with only minimal toxicity</td>
<td>CRs – 61%</td>
</tr>
<tr>
<td></td>
<td>PRs 10%</td>
</tr>
<tr>
<td></td>
<td>Median TTP 21 months</td>
</tr>
<tr>
<td></td>
<td>Median OS -50 months</td>
</tr>
</tbody>
</table>


The role of surgery in PCNSL

- To **removal of all gross tumor or debulking tumor** confers **no survival benefit** over biopsy alone.

- Survival after surgery alone is 1 to 4 months.

- The multifocal pattern of growth and the deep location of many PCNSL brain masses make complete surgical removal difficult in most patients, if not impossible.

- **Role of surgery is confined to establishment of diagnosis only** and a stereotactic biopsy is indicated for all patients with symptoms suggestive of PCNSL.
Role of HDCT and ASCT in PCNSL

Very few studies giving credibility to this strategy.

A single study of 28 patients newly diagnosed with PCNSL

Used high-dose MTX (3.5 g/m2) and high-dose cytarabine as induction treatment, followed by transplantation in 14 responders

• EFS was only 5.6 months for partial responders
• Complete responders - 9.3 months
• Median overall survival was not reached with a median follow-up of 28 months

Cheng et al - 7 patients – relapse free survival 5-42 months

Stem cell rescue may have a role in recurrent PCNSL
Soussain and colleagues – 20 patients
Three-year OS was 60% and three-year EFS rate was 53%.
## PCNSL recurrence
### Salvage Chemotherapy Studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Pts</th>
<th>ORR</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT</td>
<td>21</td>
<td>20-27</td>
<td>10.9</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>22</td>
<td>29-22</td>
<td>61.9</td>
</tr>
<tr>
<td>PCV</td>
<td>7</td>
<td>6-7</td>
<td>16</td>
</tr>
<tr>
<td>Temozolamide (TMZ)</td>
<td>23</td>
<td>6-23</td>
<td>3.5</td>
</tr>
<tr>
<td>TMZ plus Rituximab</td>
<td>15</td>
<td>8-15</td>
<td>14</td>
</tr>
<tr>
<td>Topotecan</td>
<td>15</td>
<td>6-15</td>
<td>32</td>
</tr>
<tr>
<td>HDCT plus ASCT</td>
<td>10</td>
<td>10 of 10</td>
<td>24+</td>
</tr>
</tbody>
</table>
Conclusion - PCNSL

- Rare form of extra-nodal NHL and is typically a DLBCL that is confined to the nervous system and eyes.

- The diagnosis of PCNSL is supported by CT and MRI studies as well as CSF testing, but is ultimately confirmed on the basis of stereotactic biopsy.

- Current treatment regimens are achieving long-term remissions though in only a small fraction of patients.

- Methotrexate-based, multiagent chemotherapy currently is the treatment of choice, especially in the elderly patient population.

- The optimal role and timing of WBRT in the management of newly diagnosed PCNSL patients has yet to be established.

- Minimizing the risk of neurotoxicity by deferring WBRT in patients older than age 60 is an important objective.
Primary Intra-Ocular Lymphoma - PIOL

Typically affects an older population (50-60yrs)

Two distinct forms of intraocular lymphoma.

- Arises outside the central nervous system (CNS) and metastasizes to the eye.
- The second type arises from within the CNS and eye and usually is referred to as primary CNS lymphoma (PCNSL)

Approximately 15% to 25% of PCNSL patients will have ocular involvement at the time of diagnosis
Intermediate or posterior uveitis (inflammatory process affecting the posterior segment of the eye)

Bilateral in at least 80% of cases

Affects vitreous, retina, subretinal pigment epithelium (RPE), and the optic nerve head, or any combination of these sites

Patients usually will complain of floaters and a mild decrease in vision
PIOL – Ophthalmic evaluation

Keratic precipitates

Slit lamp bi-microscopy
Showing sheets of vitreous cells

Fundus – Subretinal creamy infiltrates

Fluorescein angio
Perturbation of RPE

Diagnostic work-up

Neuroimaging
Cytologic analyses CSF

If the above are non-diagnostic a Vitrectomy usually is performed, with cytologic analysis of the vitreous biopsy
Primary Intra-Ocular Lymphoma – PIOL Therapy

Therapy for this disorder is still problematic. Radiotherapy, - minimal effect on extending survival, radiation retinopathy

Chemotherapy, with an emphasis on a therapeutic schedule that includes both systemic and intrathecal (using an Ommaya implant) agents

**Intraocular injections of methotrexate**

**PROBLEMS** - Retinal detachment, cataract, maculopathy, vitreous hemorrhage, optic atrophy, and sterile endophthalmitis and damage to the limbal stem cells
### Summary of treatment and prognosis of primary intraocular lymphoma patients published from 1989–2004

<table>
<thead>
<tr>
<th>Study [reference]</th>
<th>Treatment options</th>
<th>Regimen</th>
<th>Response (n/N)</th>
<th>Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batchelor et al, 2003 [42]</td>
<td>Systemic chemo</td>
<td>Hi-dose MTX</td>
<td>7/9 responded</td>
<td>2 deaths (intracranial progression)</td>
</tr>
<tr>
<td>Batchelor et al, 2003 [43]</td>
<td>Systemic chemo</td>
<td>Hi-dose MTX</td>
<td>2/9 refractory</td>
<td></td>
</tr>
<tr>
<td>Valluri et al, 1995 [44]</td>
<td>Systemic chemo (adjunct to intrathecal + RT)</td>
<td>MTX + ara-C</td>
<td>4/5 responded</td>
<td></td>
</tr>
<tr>
<td>Ferreri et al, 2001 [46]</td>
<td>Systemic chemo + RT chemo ± RT^a</td>
<td>Hi-dose MTX + RT chemo + RT 11, RT 3 chemo: 3 chemo + RT: 5 chemo: 4 chemo + ORT: 8 chemo + ORT + WBRT: 2</td>
<td>½ temozolomide for relapse Combination had best control</td>
<td>Death due to neurotoxicity Ocular relapse associated with shorter survival</td>
</tr>
<tr>
<td>Ferreri et al, 2002 [47]</td>
<td>Systemic chemo + RT chemo ± RT^a</td>
<td>Hi-dose MTX + RT chemo + RT 11, RT 3 chemo: 3 chemo + RT: 5 chemo: 4 chemo + ORT: 8 chemo + ORT + WBRT: 2</td>
<td>½ temozolomide for relapse Combination had best control</td>
<td>Death due to neurotoxicity Ocular relapse associated with shorter survival</td>
</tr>
<tr>
<td>Mason et al, 2003 [48]</td>
<td>Intrathecal</td>
<td>MTX + ara-C</td>
<td>3/5 complete</td>
<td>0/8 ocular relapse</td>
</tr>
<tr>
<td>Sandor et al, 1998 [39]</td>
<td>Intrathecal + chemo</td>
<td>MTX + ara-C + thiopeta + vincristine + dexamethasone MTX</td>
<td>2/5 partial</td>
<td>1/2 ocular relapse</td>
</tr>
<tr>
<td>Smith et al, 2002 [41]</td>
<td>Adjunctive intravitreal chemo</td>
<td>MTX</td>
<td>22/22 responded 6/22 recurrence (retreatment with response)</td>
<td>6/16 deaths (intracranial progression)</td>
</tr>
</tbody>
</table>
Primary Intra-Ocular Lymphoma – PIOL Summary

PIOL is a rare subset of PCNSL.

It typically masks as a chronic ocular inflammatory disease that is resistant to corticosteroid therapy.

The diagnosis can be challenging, and it requires the immediate processing of ocular biopsy specimens.

Treatment is still a dilemma, and future studies are aimed at delineating the underlying tumor biology and thus developing better-targeted therapies.
Thank You