Primary CNS Lymphoma

- >90% Large B-Cell
- Prognosis generally poor relative to localized, large cell lymphomas outside CNS
- BCL6+/MUM1+
- Immunophenotype
- No role for anthracycline-based therapy

Major Treatment Paradigms in PCNSL

MTX: Heightened Responsiveness to HD-MTX
- 30-60% rate of CR
- 52% rate of CR with MTX 8 gm/m²
  (Batchelor et al., JCO, 2003)

WB-XRT: 90% Response to WB-XRT (45 Gy)
- 80% rate of Neurotoxicity in Patients Age>60
  (Abrey et al., JCO, 1988)

High-Dose Chemotherapy
- HD-AC/VP16: High Rate of Response in Recurrent CNS Lymphoma after MTX Failure
- Preliminary Evidence for Efficacy of ASCT at Relapse
  (Soussain et al., JCO, 2001)
**RTOG 93-10 Multicenter Trial of Memorial Sloan-Kettering Regimen**
(Combined-Modality Therapy; N=102)

**Durable Response in PCNSL Without WB-XRT**

“MTR” intensive Methotrexate plus Temozolomide and Rituximab followed by high-dose consolidation “EA” (cytarabine-infusional etoposide)

**MTR-EA Consolidation at UCSF (2001-2006)**

N = 25 patients
Major Challenges in PCNSL

I. Delineation of Molecular and Pathologic Risk Groups
II. Development of Molecular Tools to Facilitate Early and Noninvasive Diagnosis
III. New Strategies to Overcome Drug Resistance

Molecular Distinctions of Primary CNS Lymphoma vs. Nodal Diffuse Large B-Cell NHL

Rubenstein et al., Blood, 2006

IL-4 Signaling and Prognosis in PCNSL
Diffusion-Weighted MR Imaging of Brain Tumors

Water diffusion is altered in distinct pathologic processes and can be quantified by MRI.

Apparent Diffusion Coefficient (ADC) correlates with cell density within tumors.

Guo et al., Radiology 2002; 224: 177-183.

Apparent Diffusion Coefficient (ADC) Measurements in PCNSL at Diagnosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>ADC (x10^-6)</th>
<th>T1</th>
<th>T2</th>
<th>T2*</th>
<th>Diffusion</th>
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<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>1.5</td>
<td>1.8</td>
<td>1.9</td>
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<tr>
<td>2</td>
<td>1.3</td>
<td>1.2</td>
<td>1.6</td>
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<td>1.5</td>
<td>1.4</td>
<td>1.8</td>
<td>1.9</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Examples of Low vs. High ADC in PCNSL Tumors at Diagnosis
Diffusion-Weighted Imaging and Outcome in PCNSL

Barajas, Rubenstein et al., Am. J Neurorad. 2010

Two Patients with midbrain lesions. Dx ?

Proteomic Analysis of CSF Using 2D-LC/MS
IDENTIFICATION OF DIFFERENTIALLY EXPRESSED CSF PROTEINS

CSF ATIII > 1.2 µg/ml  75% sensitivity; 98% specificity for cancer
CSF ATIII = 0.5 µg/ml  
CSF ATIII = 2.1 µg/ml

Neurosarcoid  
CNS Lymphoma

Phase I Study Intraventricular Rituximab in patients with Refractory CNS Lymphoma

- Ten subjects, HIV negative, refractory CNS lymphoma
- Nine planned intraventricular injections of rituximab (10-50 mg)

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Re-stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>IT Rituximab</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

- Goals:
  1) Define safety, maximum tolerated dose
  2) Define pharmacokinetics of intraventricular MAb administration
  3) Insight into molecular basis of rituximab action, resistance

Rubenstein et al., JCO, 2007
Phase I Multicenter Study To Evaluate Dose Escalation Safety and Pharmacokinetics of Intraventricular Rituximab in Combination with Methotrexate in Patients with Recurrent or Refractory CNS and Intraocular Lymphoma

- 10 and 25 mg IT rituximab plus IT MTX
- Open at UCSF and Harvard (MGH/Dana Farber)
- No DLT yet identified
- Longest response 8 months

Summary

I. AE Cytarabine-Etoposide Consolidation Appears Highly Active: Long-term progression-free survival possible without WBXRT in PCNSL.

II. Definition of molecular subgroups of risk in PCNSL will facilitate evaluation and interpretation of novel clinical strategies.

III. Active Program at UCSF in CSF Biomarkers to Facilitate Dx.

III. Systematic evaluation of novel pharmacologic agents in preclinical models is essential to develop rational approaches to overcome drug resistance in PCNSL.

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NCI, Leukemia & Lymphoma Society, ASCO, ACS, G&P Foundation
Survival < 6 mo  
Survival > 6 mo

GENE EXPRESSION PROFILE ASSOCIATED WITH VERY SHORT SURVIVAL IN PRIMARY CNS LYMPHOMA

- CSF ATIII > 1.2 µg/ml  75% sensitivity; 98% specificity for cancer
CSF ATIII and Prognosis

Intratumoral water diffusion and outcome in PCNSL
Progression-Free Survival: MTR – Ara-C/VP16: UCSF Experience

MTR – Ara-C/VP16  Accrual Near Completion: CALGB 50202
Molecular Distinctions of Primary CNS Lymphoma vs. Nodal Diffuse Large B-Cell Lymphoma

Blood, 2006
IDENTIFICATION OF DIFFERENTIALLY EXPRESSED CSF PROTEINS

Example of CSF ATIII as CSF Biomarker

CSF ATIII > 1.2 µg/ml  75% sensitivity; 98% specificity for cancer

CNS Lymphoma Model

Biologic Targets In Primary CNS Lymphoma

Pim-1, Pim-2
Interleukin-4, JAK-2, STAT6

Kadoch et al., Clinical Cancer Research