CNS involvement of lymphomas: when and how to treat?

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Hematology-Oncology fellow
Case 1

• Mr. L is a 67 yo M with 6-7 years of worsening back pain, no neurological symptoms or deficits
• A page from American Lake VA for a critical findings of spinal mass invading spinal canal on L spine MRI
• Biopsy confirmed DLBCL, stage IV, IPI=4 (high)

**Questions:**
• Does he have CNS involvement?
• Does he need LP?
• Does he need CNS treatment? If yes, what treatment?
• What is his risk of CNS relapse?
CNS lymphomas

• Synchronous brain and systemic lymphoma at diagnosis:
  - Involve the brain parenchyma, intraocular compartment, cranial nerves, leptomeninges, spinal cord

• Secondary CNS lymphoma (SCNSL):
  - Isolated CNS relapse
  - CNS involvement with systemic relapse or progression

• Primary CNS lymphoma (PCNSL): limited to the brain parenchyma, intraocular compartment, cranial nerves, leptomeninges, spinal cord
CNS workup: Who and When?

NCCN Guidelines (grade 2A recommendations)

B cell lymphoma:
- **DLBCL**: consider if high risk according to prognostic model (CNS-IPI), HIV lymphoma, testicular, double expressor lymphoma
- **Burkitt lymphoma**: all regimen include CNS prophylaxis/therapy
- **MCL**: for blastic variant or CNS symptoms

T cell Lymphoma: intrathecal chemotherapy is recommended

CNS workup in DLBCL: Who and When?

Prognostic Model to Assess the Risk of CNS Disease (CNS-IPI):
- Age >60 years
- Serum LDH > normal
- Performance status >1
- Stage III or IV
- Extranodal involvement >1 site
- Kidney or adrenal gland involvement

Low risk 0-1
Intermediate-risk 2-3
High-risk 4-6
CNS workup: Who and When?

2,164 patients with aggressive B-cell lymphomas (80% DLBCL) were enrolled in the German High-Grade Non-Hodgkin Lymphoma Study Group and the MabThera International Trial were analyzed for occurrence of relapse/progression in the CNS. Validated in an independent data set of 1,597 patients with DLBCL in the British Columbia Cancer Agency Lymphoid Cancer database.

CNS workup: Who and When?

2-year rates of CNS disease

DSHNHL/MlnT
- low-risk (46%): 0.6% (CI, 0-1.2%)
- intermediate-risk (41%): 3.4% (2.2-4.4%)
- high-risk (12%): 10.2% (6.3-14.1%)

BCCA
- low-risk: 0.8% (CI, 0.0-1.6%)
- intermediate-risk: 3.9% (2.3-5.5%)
- high-risk: 12.0% (7.9-16.1%)

CNS International Prognostic Index: recommendation

- Close to 90% of patients = low- and intermediate-risk groups; CNS relapse risk <5%; they may be spared any diagnostic and therapeutic intervention.

- Patients in the high-risk group have a >10% risk of CNS relapse; should be considered for CNS-directed investigations and prophylactic interventions.

- Testicular involvement: almost all patients received IT MTX in the German studies; only 10% of patients had CNS prophylaxis in the BCCA database. Cannot exclude testicular involvement as a risk factor for CNS relapse.

- The CNS-IPI was developed for DLBCL, its applicability in other lymphomas is unknown.
Burkitt lymphoma

• In the sporadic form of BL in adult patients, CNS involvement is reported in ~15% of patients.

• IT chemo and HD MTX and cytarabine, with or without the addition of cranial irradiation, have dramatically reduced the risk of CNS relapse to ~5%.

Double-hit vs double-expresser lymphomas

- The dual expressers have a cumulative risk of CNS relapse of 9.7% compared with 2.2% in non–dual expressers
- Within the high-risk CNS-IPI, dual expresser have a 2-year risk of CNS relapse of 22.7% compared with 2.3%
- Within the CNS-IPI intermediate-risk group, dual expresser have a higher risk of CNS relapse (11% vs 3.2%)

TCL: OS IN PTCL BY CNS INVOLVEMENT
CLINICAL FEATURES OF PATIENTS WITH CNS INVOLVEMENT

Of the 275 patients with peripheral TCL, 17 (6.2%) patients had CNS involvement

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (N=17)</th>
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<tbody>
<tr>
<td>Treatment status at the time of CNS involvement</td>
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<tr>
<td>Before or during first-line treatment</td>
<td>4 (23.5%)</td>
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<tr>
<td>During or after salvage treatment</td>
<td>13 (76.5%)</td>
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<tr>
<td>Prophylactic IT chemotherapy*</td>
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<tr>
<td>Yes</td>
<td>4 (30.8%)</td>
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<tr>
<td>No</td>
<td>9 (69.2%)</td>
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<tr>
<td>CNS involvement pattern</td>
<td></td>
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<tr>
<td>Lymphomatous meningitis</td>
<td>14 (82.4%)</td>
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<tr>
<td>Intraparenchymal</td>
<td>2 (11.8%)</td>
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<tr>
<td>Combined</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td></td>
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<tr>
<td>Asymptomatic</td>
<td>10 (58.5%)</td>
</tr>
<tr>
<td>Cauda equina syndrome</td>
<td>3 (17.6%)</td>
</tr>
<tr>
<td>Acute meningitis</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>Visual changes</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Mentality change</td>
<td>1 (5.9%)</td>
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</tbody>
</table>

*N=13
T cell lymphoma: who to screen for CNS involvement?

Prior retrospective series suggest that the rate of CNS involvement in PTCL ranges from 2% to 9%

Risk factors that increase the risk of CNS relapse include:
- Histology of ATLL
- high-intermediate and high IPI
- more than one extra nodal site: sinus, scalp, etc.

How I treat CNS lymphomas

CNS-IPI low (0, 1, factors) or intermediate (2, 3, factors) w/o testicular, renal or adrenal inv.

~ 90% of patients with a 2-year-rate of <5%

No CNS diagnostics
No prophylaxis

CNS-IPI high (>4 risk factors) and / or testicular, renal or adrenal inv.

~ 10% of patients with a 2-year-rate of ≥10%^a

CNS directed diagnostics^b

Consider CNS prophylaxis^c

CNS treatment protocol

CNS prophylaxis

• BCCA: 1732 patients with DLBCL treated with R-CHOP. 70% of CNS relapses involved parenchyma and 30% were isolated to the leptomeningeal compartment.

• Prophylaxis strategies must consider drugs that deeply penetrate into the brain.

• Primary CNS prophylaxis traditionally consisted of IT MTX, IT Ara-C, IT hydrocortisone, or combinations of these drugs

• IT chemotherapy does not reach measurable concentrations in the brain parenchyma except for areas directly adjacent to the brain.
IT CNS prophylaxis: does it help?

Fig. 2 Kaplan–Meier estimated CNS relapse-free survival by IT among 203 patients in “high-risk group”. $P$ value=0.981

IT CNS prophylaxis: should it be considered?

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Systemic/IT Treatment</th>
<th>CNS Prophylaxis Indications</th>
<th>CNS Relapse (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmitz et al., 2012</td>
<td>2196 (1576 w/o R, 620 with R)</td>
<td>(R)-CHOEP&lt;sup&gt;a&lt;/sup&gt; IT MTX</td>
<td>BM, testis, head, sinuses, orbits, oral cavity, tongue, and salivary glands</td>
<td>2.6 (all pt)</td>
<td>.386</td>
</tr>
<tr>
<td>Boehme et al., 2009</td>
<td>1222 (612 w/o R, 610 with R)</td>
<td>(R)-CHOP IT MTX</td>
<td>BM, testis, head, sinuses, orbits, oral cavity, tongue, and salivary glands</td>
<td>2.5 (w/o prophylaxis) 4.4 (with prophylaxis)</td>
<td>NS</td>
</tr>
<tr>
<td>Kumar et al, 2012</td>
<td>989 (all with R)</td>
<td>R-CHOP IT MTX ± IT Ara-C, IV MTX (28%)</td>
<td>At the discretion of investigator</td>
<td>2.1 (w/o prophylaxis) 10.9 (with prophylaxis)</td>
<td>.007</td>
</tr>
<tr>
<td>Tai et al, 2011</td>
<td>499 (179 w/o R, 320 with R)</td>
<td>(R)-CHOP IT MTX</td>
<td>&gt;1 ENS, orbits, sinuses, breast, testis, bone, BM</td>
<td>5 (w/o prophylaxis) 11 (with prophylaxis)</td>
<td>NR</td>
</tr>
<tr>
<td>Tomita&lt;sup&gt;9&lt;/sup&gt;</td>
<td>322 (all with R)</td>
<td>R-CHOP IT MTX</td>
<td>↑ LDH, bulk &gt;10 cm, PS ≥2, BM, nasal, bone, breast, skin, testis</td>
<td>2.8 (w/o prophylaxis) 7.5 (with prophylaxis)</td>
<td>.14</td>
</tr>
<tr>
<td>Arkenau et al, 2007</td>
<td>259 (177 w/o R, 62 with R)</td>
<td>(R)-CHOP (R)-PmitCEBO IT MTX ± Ara-C</td>
<td>BM, testis, sinuses, orbits, bone, blood</td>
<td>1.1 (CI, 0%-2.5%) 2 pt w/o prophylaxis 1 pt with prophylaxis</td>
<td>NR</td>
</tr>
<tr>
<td>Guirguis et al, 2012</td>
<td>214 (all with R)</td>
<td>R-CHOP IT MTX (25 pt), IV MTX (17 pt)</td>
<td>↑ LDH, &gt;1 ENS, testes, epidural, sinuses, or skull</td>
<td>2 (w/o prophylaxis) 1.9 (with prophylaxis)</td>
<td>NR</td>
</tr>
</tbody>
</table>
Systemic CNS prophylaxis

- HD-MTX: potentially even distribution of therapeutic drug levels throughout all CNS compartments
- Systemic HD-MTX or cytarabine showed fewer CNS recurrences
- European Society of Medical Oncology (ESMO) guidelines: HDMTX as the preferred type of CNS prophylaxis in high-risk patients, high-risk IPI and for those with testicular or adrenal/renal involvement
- 3 to 3.5 g/m2 as the preferred CNS prophylaxis because 1.5 g/m2 may not achieve adequate CSF drug levels.
- Prophylaxis should be considered in patients with high-risk CNS-IPI particularly if dual expressers. Patients with testicular, renal, or adrenal involvement should receive prophylaxis regardless of their CNS-IPI.
Case 2

• 68 yo F with diagnosis of mycosis fungoides, with large cell transformation
• underwent nonmyeloablative matched unrelated donor allogeneic SCT in 2010.
• Disease recurred shortly after the transplant.
• Treated with a short course of pralatrexate and focal radiotherapy to the right shin in 2011, with resolution.
• Free of lymphoma for 5 years.
• She was diagnosed with isolated CNS recurrence in early 2016,
• She was treated by Dr. Mrugala with 12 cycles of HD-MTX (last cycle 11/2016).
• Most recently, she also received gamma knife therapy to occipital metastases.
• Now with confusion, memory loss.
MRI 2/6/2017: what’s next?
Case 3

• 61 yo F with alpha beta hepatosplenic T-cell lymphoma (initial diagnosis in 2009).
• Underwent hyper-CVAD, followed by myeloablative SCT from HLA-matched sister.
• Disease relapse at 4.5 years posttransplant with perforated small bowel related to tumor mass.
• Disease progression despite resection of mass and multiple chemo.
• She was also discovered to have lymphomatous meningitis with cauda equina syndrome in 6/2015, managed by Dr. Chamberlain. s/p XRT to sacral canal with persistent neurologic deficits. Disease persist s/p IT MTX. Ommaya placed for intraventricular thiotepa followed by topotecan.
• Salvage therapy with significant bone marrow suppression, complicated by HSV infx and CMV viremia.
CNS lymphomas

- **Synchronous brain and systemic lymphoma at diagnosis**

- **Secondary CNS lymphoma (SCNSL):**
  - Isolated CNS relapse
  - CNS involvement with systemic relapse or progression

- **Primary CNS lymphoma (PCNSL):** limited to the brain parenchyma, intraocular compartment, cranial nerves, leptomeninges, spinal cord
CNS lymphomas

- Rates of CNS involvement over a 5-yr period in aggressive lymphomas: ~5%
- CNS involvement result in dramatically shortened OS: often < 6 mon
- Clinical features:
  - **Lymphomatous meningitis**: more common, typically present within the 1st year
  - **Parenchymal brain metastasis**: less common
  - **Intramedullary spinal metastasis**: rare. May develop when a tumor in the subarachnoid space grows along nerve roots into the spinal cord in the setting of widespread metastatic disease
  - **Neurolymphomatosis**: Uncommon. Direct involvement of the peripheral nerves, typically the cranial nerves and spinal nerve roots

Secondary CNS lymphoma

- SWOG 8516: CNS relapses tend to occur earlier than systemic relapses
- Median onset of CNS relapse: within 5.4 months of initial therapy
- Median survival after diagnosis of SCNSL: 2.2 months compared with 9 months for non-CNS relapse
- Recent meta-analysis of almost 5000 patients with DLBCL treated with R-CHOP or equivalent anthracycline-based chemotherapy showing a risk of CNS recurrence of ~5%

2nd CNS lymphoma: does chemo regimen matter?

- **RICOVER-60 trial**: 1112 patients with aggressive B-cell lymphoma (81.6% DLBCL), 2-year incidence of CNS disease was 6.9% after CHOP and 4.1% after R-CHOP.

- **British Columbia Cancer Agency (BCCA)**: similar trend in a higher risk population (3-year risk, 9.7% R-CHOP vs 6.4% CHOP).

- **(R)-ACVBP regimen** used in high-risk DLBCL is combined with an intensive consolidation phase including IV MTX, etoposide, ifosfamide, and cytosine-arabinoside (all cross the BBB), low frequency of CNS disease (<1%) even w/o rituximab.

- The phase 3 study comparing DA-EPOCH-R with R-CHOP has been completed and the results are eagerly awaited.

CNS directed treatment: when and how?

• M–R-CHOP: HD-MTX (3-8 g/m2) with leucovorin rescue q2wk for 8 cycles plus standard dose R-CHOP q3wk for 6 cycles.

• DA-EPOCH-R with mid-cycle HD-MTX (DA-EPOCH-R/HD-MTX)

• EA consolidation: CR in both CNS and systemic compartments, and have adequate organ function.
CNS directed treatment: when and how?

Retrospectively analyzed 18 patients (4 untreated and 14 relapsed) with systemic lymphoma with CNS involvement who received methotrexate and cytarabine-based multiagent chemotherapy (modified Bonn protocol). Study in Japan.

Complete response: 56%
Partial responses: 22%
The 1-year overall survival (OS): 81%
1 yr progression-free survival (PFS): 39.2%

Table 1. Modified Bonn chemotherapy protocol

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tr>
<td>Cycle A</td>
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<tr>
<td>Methotrexate IV², 3 g/m²</td>
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<tr>
<td>Vincristine IV², 2 mg²</td>
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<tr>
<td>Ifosfamide IV², 800 mg/m²</td>
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<tr>
<td>Dexamethasone IV², 16.5 mg</td>
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<tr>
<td>IT-triple²</td>
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<td>Cycle B</td>
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<tr>
<td>Methotrexate IV², 3 g/m²</td>
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<tr>
<td>Vincristine IV³, 2 mg²</td>
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<tr>
<td>Cyclophosphamide IV², 200 mg/m²</td>
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<tr>
<td>Dexamethasone IV², 16.5 mg</td>
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<td>IT-triple²</td>
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<td>Cycle C</td>
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<td>Cytarabine IV², 2 g/m² 12-hourly</td>
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<td>Vindesine IV³, 5 mg</td>
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<td>+</td>
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<tr>
<td>IT-triple³</td>
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IV, intravenously; PO, orally; IT, intrathecal chemotherapy.
* 24-h infusion; b 30-min infusion; c 3-h infusion; d 1-h infusion; e IT-triple (methotrexate 15 mg + cytarabine 40 mg + prednisolone 10 mg).

CNS treatment: other regimen?

• **HOVON 80 phase 2 study**
  
• Treatment consisted of 2 cycles of R-DHAP alternating with high-dose MTX combined with intrathecal rituximab.

• Responding patients received a third R-DHAP-MTX cycle followed by autologous SCT.

• In patients with persistent cerebrospinal fluid lymphoma after cycle 1, the intrathecal rituximab was replaced by intrathecal triple therapy, with MTX, cytarabine, and dexamethasone.

• This treatment regimen did not result in a major improvement of outcome of secondary CNS lymphoma, especially when concurrent systemic disease was present.

CNS treatment: other options?

• Small molecule therapeutics such as ibrutinib and lenalidomide cross the BBB
• Limited studies show efficacy in primary CNS lymphoma or mantle lymphoma with CNS involvement.
• Ongoing phase 3 studies comparing R-CHOP plus ibrutinib or R-CHOP plus lenalidomide versus standard R-CHOP in DLBCL.
• The DSHNHL will start a phase II study using R-CHOEP plus ibrutinib in young high-risk patients (age-adjusted IPI 2 or 3) with DLBCL.
ASCT
29/54 pt with DLBCL and CNS involvement have received ASCT.

HDT-ASCT may only be applicable to selected patients with secondary CNS DLBCL.
Case 4

- Mr. Y is a 55 yo M, borderline homeless, who initially presented with seizure in 7/2015
- 9/2015: MRI Brain showed a large enhancing mildly T2 hypointense extraaxial mass
- Brain resection confirmed MALT, CD20+
- A consult from neurology to for BM biopsy
- All other workup including BM biopsy negative for lymphoma
Case 4

• What are his treatment options?

A. Rituximab
B. Field radiation
C. HD MTX
D. Surveillance
CNS lymphomas

• Synchronous brain and systemic lymphoma at diagnosis

• Secondary CNS lymphoma (SCNSL): concomitant systemic, and CNS localization of lymphoma, often within the leptomeningeal compartment.
  - Isolated CNS relapse
  - CNS involvement with systemic relapse or progression

• Primary CNS lymphoma (PCNSL): limited to the brain parenchyma, intraocular compartment, cranial nerves, leptomeninges, spinal cord
PCNSL

- Rare brain tumor
- 1900 new cases each year in US
- 3% of all newly diagnosed brain tumors
- 2% to 3% of all cases of NHL
- The Surveillance, Epidemiology and End Results (SEER) database: incidence may be increasing among patients age > 65
PCNSL

• 95% of PCNSL tumors are CD20+, DLBCL
• less common histologies include T-cell PCNSL (2%), Burkitt, lymphoblastic, and intraparenchymal marginal zone lymphoma.
• 20% of PCNSL cases present with intraocular involvement
Prognosis

• The International Extranodal Lymphoma Study Group: 5 parameters associated with poor prognosis in PCNSL
  - age older than 60 years
  - ECOG>1
  - elevated LDH
  - high CSF protein concentration
  - tumor location within the deep regions of the brain (periventricular, basal ganglia, brainstem, and/or cerebellum)

• 0-1: 2 yr OS 80%
• 2-3: 2 yr OS 48%
• 4-5: 2 yr OS 15%
Diagnostic studies

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
ASCT, autologous stem cell transplant; CR, complete response; EA, etoposide-cytarabine; HSV, herpes simplex virus; MT-R, combination HD-MTX, temozolomide, and rituximab (rituximab is omitted for T-cell lymphomas); PCP, Pneumocystis jiroveci pneumonia; PD, progressive disease; PR, partial response; SD, stable disease; WBRT, whole-brain radiotherapy
Induction regimen

• The first randomized trial: by the United Kingdom Medical Research Council to investigate whether the addition CHOP after WBRT would prolong OS. The trial was terminated due to poor accrual. Addition of CHOP to WBRT does not improve OS.

• HD-MTX as a standard component of PCNSL treatment.

• MT-R

• R-MP for age>65yo: rituximab (375 mg/m², days 1, 15, 29), high-dose methotrexate (3 g/m² days 2, 16, 30), procarbazine (60 mg/m² days 2-11)

• WBRT alone or in combination with steroids without chemotherapy as first-line treatment is of limited effectiveness.

Whole brain radiation (WBR)

• HD-MTX represents the most accepted standard of care induction therapy for newly diagnosed PCNSL.

• When HD-MTX is given with WBRT for consolidation delayed neurotoxicity can be an important complication, particularly in elderly patients.

• In the RTOG 93-10 phase 2 trial, delayed neurotoxicity including memory deterioration, personality change, gait disturbance, or urinary incontinence emerged as severe complications in ~15% of patients.

• Retrospective series of 185 patients found the overall 5-year incidence of developing neurotoxicity was estimated to be 30%

• WBRT may be deferred until relapse without compromising survival.

Neurotoxicity

IT CHEMO

HD CHEMO

XRT

SCT

IS
IT chemo

• No prospective randomized evidence on the use or benefits of intrathecal chemotherapy; therefore its application remains controversial

• Retrospective data: additional IT methotrexate and cytarabine showed no additional benefit when given with HD-MTX

• Two single-arm studies reported an additional benefit (Median OS 14.3 months, and 1-year PFS 40%) for intraventricular MTX, corticosteroid, and additional cytarabine

• the European Guidelines do not advocate for its addition as part of standard treatment

Surgery: is it an option?

- German PCNSL Study Group-1 (GPSG-1) Trial:
  - aggressive resection of CNS lymphoma correlated with improved PFS

- Columbia University Medical Center between 2000 and 2015
  - The overall complication rate was 17.2% after resection, and 28.2% after biopsy.
  - Patients who underwent resection were less likely to have multiple (46.5% v. 27.6%) or deep lesions (70.4% v. 39.7%).

- In individualized cases, particularly well-circumscribed lesions with significant mass effect, aggressive surgical cytoreductions:
  - provide immediate relief of mass effect
  - facilitate the rapid tapering of glucocorticoids
  - eliminate cell populations with drug resistance potential

Consolidation: EA

- multicenter, single-arm, phase 2 study, 44 PCNSL patients were treated with MT-R; patients who achieved CR were consolidated with a combination of HD-Ara-C and etoposide.
- median follow-up of 4.9 years, the 2-year PFS was 57% and the 4-year OS was 65%.

ASCT: for refractory or relapsed cases?

- The International Extranodal Lymphoma Study Groups (IELSG) 32: The MATRix regimen (HD-MTX, HD-ARAC, thiotepa, and rituximab) was associated with the best overall results with an ORR of 87% and a 2-year PFS of 62%.

- Phase II study enrolled 30 patients (<65yo) to HDC-ASCT followed by WBRT for newly diagnosed PCNSL. 5-yr OS rate of 87% for pts who received the full study (23/30).

- HDC–ASCT is an effective treatment for select patients with refractory/relapsed PCNSL.

- Further evidence including ongoing trials comparing HD-MTX to HDC–ASCT will determine the role of the latter as a first line treatment strategy from PCNSL.

Conclusion

• Treatment of CNSL requires a multidisciplinary approach

• Despite development and availability of several treatment guidelines, an accepted standard approach is currently not well established.

• Key decisions and recommendations should be framed in the context of a multidisciplinary team
THANK YOU FOR LISTENING!