Primary CNS Lymphoma

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Outline

- Case Presentation
  - Clinical Presentation
  - Workup
  - Management
  - Follow-up

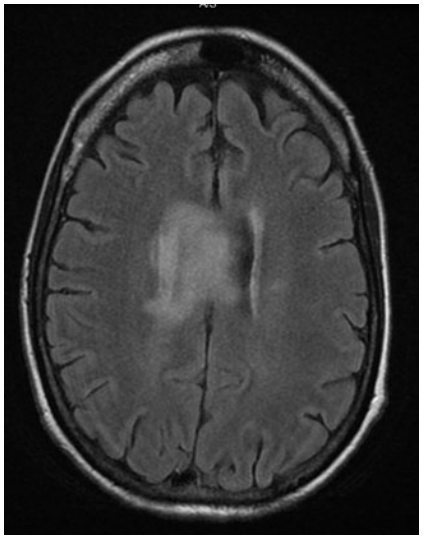
- Background
- Presentation
- Workup
- Prognosis
- Management
  - Induction Therapy
  - Consolidation Therapy
  - Maintenance
  - Salvage Therapy

Case: Clinical Presentation

- 53-year-old woman presents to ED by PCP referral for increasing confusion, memory loss, and vertigo over the last couple of weeks. Concern for lupus flare.
  - **PMHx:** systemic lupus erythematosus, CKD IV, rheumatoid arthritis, intermittent asthma, fibromyalgia
  - **PSH:** non-contributory
  - **FH:** scleroderma (sister), rheumatoid arthritis (cousin)
  - **SH:** no history of substance use
  - **Pertinent Medications:** **hydroxychloroquine, methotrexate (2.5mg, 3xweekly)**
  - **Allergies:** none
  - **Physical Examination:** vitals wnl, well-appearing, no lymphadenopathy, AAOx3, no cranial nerve deficits, no sensory deficits, normal muscle tone, gait abnormal with impaired balance, impaired cognition, and short-term memory, MMSE 26/30, MOCA = 18/30 (areas of difficulty including orientation, STM, and visual-perceptual deficits), KPS = >90%

Case: Diagnostic Workup

- **Initial imaging**, MRI wo contrast: diffusion restriction within L corpus callosum, T2 signal hyperintensity within R caudate and lentiform nuclei.
- **Lumbar puncture**: elevated total nucleated cells (268) of which 80% were described as pleomorphic large lymphocytes concerning for CNS involvement of lymphoma. Flow cytometry shows CD45, CD19, CD20 and is consistent with **NHL-DLBCL**
- **No surgical biopsy was performed.**



Initial scan – T2 MR

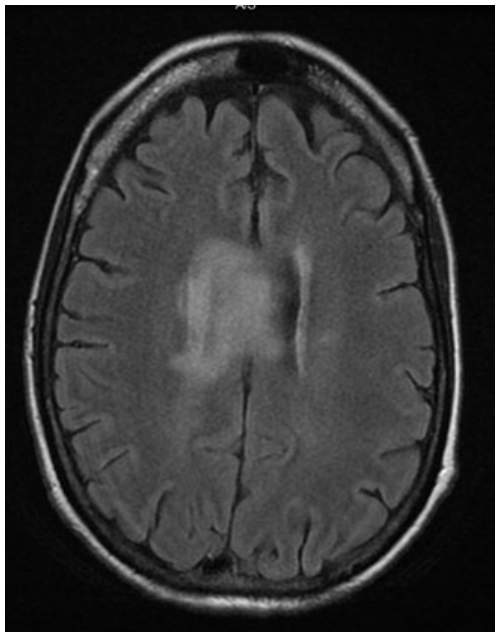
- **Labs**: WBC wnl, Hgb 9.8, LDH wnl, GFR 19, HIV NR, HBV NR, EBV NR
- **Ophthalmology**: slit-lamp exam normal
- **CT chest/abdomen/pelvis wo contrast:** no signs of extracranial involvement
- **Bone Marrow Biopsy**: no malignant cells

Case: Management

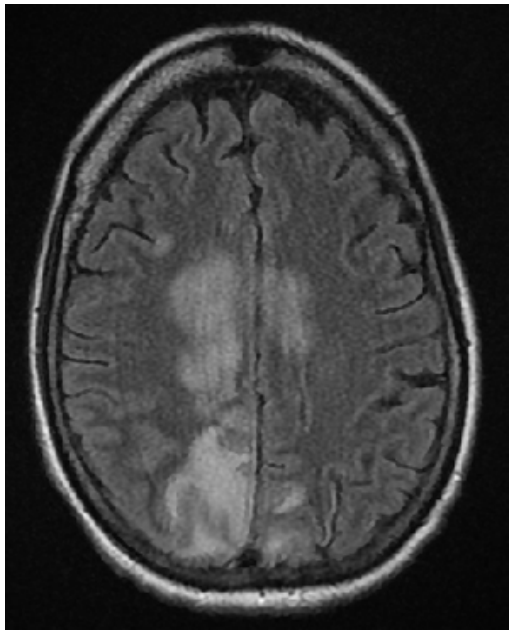
- **Induction chemotherapy**: initiated MTX-based polychemotherapy with rituximab/MTX/TMZ (R-MT). MTX at reduced dose for CKD IV.
  - Repeat LP was negative for malignant cells but follow-up MRI showed progression. Shown next slide. Patient developed rapidly progressive chemotherapy-induced ataxia, lethargy, and symptoms of increased intracranial pressure.
  - IT rituximab initiated due to treatment limitations in setting of CKD IV.
- **Pt treated with WBRT and immunotherapy:** no longer a candidate for previously planned consolidation (HDC-ASCT) given progressive disease and CKD IV.
  - **Salvage radiotherapy:** **WBRT 39.6 Gy/ 1.8 Gy per fraction** with dexamethasone taper. After completion of WBRT, 1-month follow-up MRI showed a drastic reduction in gross disease. Shown next slide.
  - **Maintenance immunotherapy**: initiated Nivolumab with close follow-up for persistent disease.

Case: Imaging

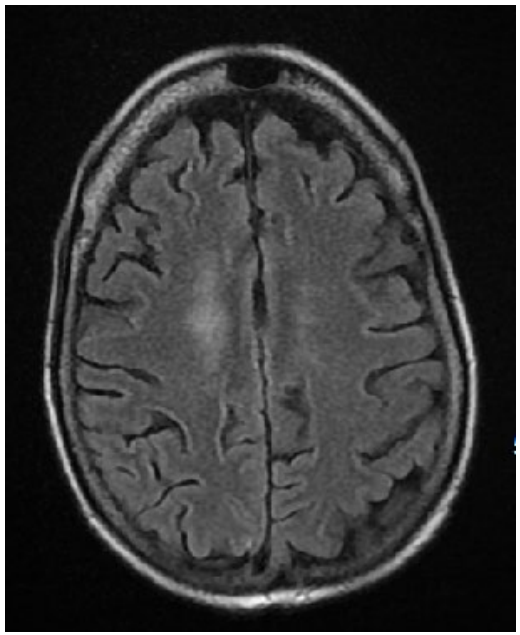
T2 FLAIR MRI without contrast. Contrast was not administered due to the history of CKD stage IV.



Initial scan



Progressive disease following induction chemotherapy



Significant response following salvage WBRT

Case: RT Treatment Planning

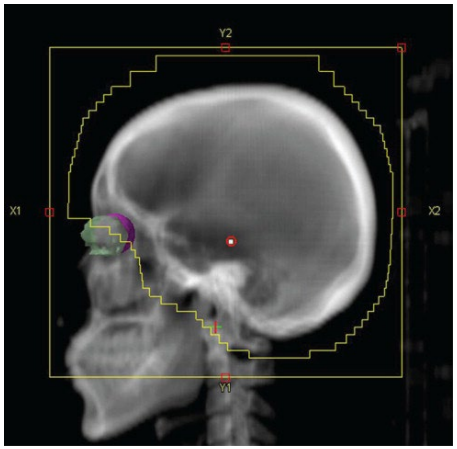
Target Delineation

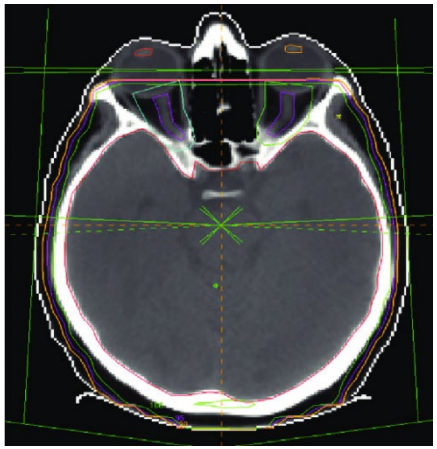
- CTV: whole brain + 1-2 cervical vertebra + posterior aspect of eyes.
- If ocular involvement is found, include the entirety of both eyes in CTV.
- There is no consensus guidelines on GTV volumes and there is no consensus on tumor boost recommendations.
- For boost delineation consider contouring area of contrast enhancement seen on T1-post contrast.

ILROG Guidelines (Yahalom *et al*, 2015).

Plan Evaluation

- Use opposed laterals with flash anterior and posterior.
- Bottom of field is inferior C2 border.
- Block eyes if no ocular involvement.
- Hippocampal avoidance not recommended given diffuse nature of CNS lymphoma as a whole brain disease.

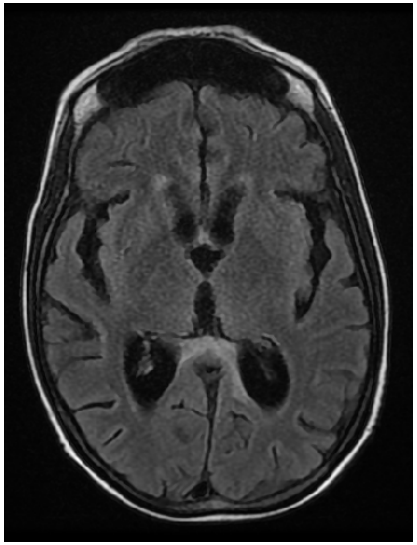




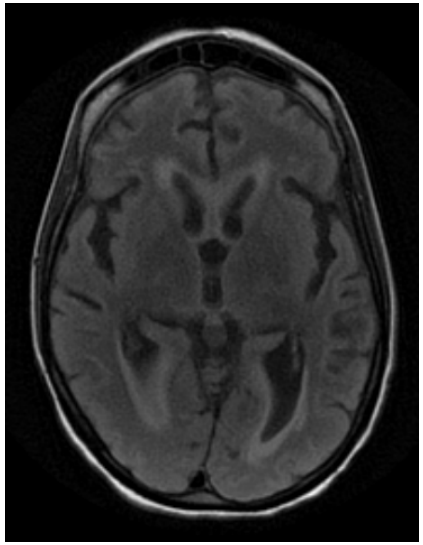
Case: Follow-up

- During immunotherapy, patient continued to decompensate with multiple infections, failure-to-thrive, and worsening neurologic function. Follow-up MRI 2-months after RT completion and initiation of immunotherapy showed worsening disease progression. Patient was referred to hospice and ultimately passed away 7 months after diagnosis following several failed lines of therapy, including systemic chemotherapy, intrathecal rituximab, radiation therapy, and immunotherapy.

- Outcome is highly dependent on the degree of response and tolerance to a prolonged regimen of HD-MTX. Good response/tolerance warrants consolidative methods. Poor response/tolerance results in salvage radiation and palliative methods with high likelihood of progression within a few months, as demonstrated here.



Significant response following salvage WBRT



Progressive disease following maintenance immunotherapy

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Background

Epidemiology:

- PCNSL occurs in 4 per 1,000,000 people per year and accounts for 4% of all primary intracranial neoplasms and 4-6% extra-nodal lymphomas.
- Most common risk factor: **immunodeficiency**
- 2:1 male predominance overall; 9:1 male predominance in immunocompromised patients.
- Median age 50-60 years with increasing incidence in elderly population 65+.

Pathology:

- Majority of cases are **diffuse large B-cell lymphoma,** activated B-cell/non-germ center subtypes, which are associated with increased frequency in B-cell pathway mutations. Associated with worse prognosis compared to systemic DLBCL.
- DLBCL positively stains for B-cell markers, CD20, CD45, MUM1/IRF4, BCL6, MYC.

HIV/AIDS:

- HIV accounts for 15% of NHL cases with majority associated with EBV. HIV-associated PCNSL is classified as an AIDS-defining-illness and is much more difficult to treat. Incidence has decreased since initiation of combined-ART.

Presentation

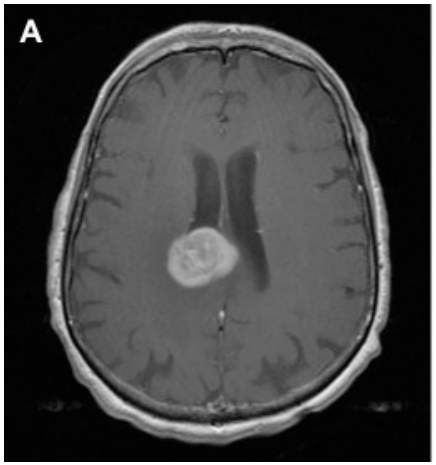
- **Symptoms:**
  - Focal Neurologic Deficits (70%), nonspecific neurocognitive or behavioral changes (43%), increased intracranial pressure (33%), decreased visual acuity, blurry vision, floaters (20%), seizures (14%), B symptoms (rare)
- **Areas of involvement:**
  - Supratentorial (87%), frontoparietal region (39%), eyes (15-25%), CSF (7-42%), spinal cord (rare)
- **Multifocality:**
  - Single brain lesion (66%) with suspected **microscopic multifocality** in immunocompetent (50%) and immunocompromised (100%) patients.
- **DDx:**
  - Secondary CNS lymphoma, PTLD, high-grade glioma, melanoma, or carcinoma, infection (abscess, toxoplasma) vascular (hemorrhage, infarction) autoimmune (multiple sclerosis, sarcoid)

Workup Pearls

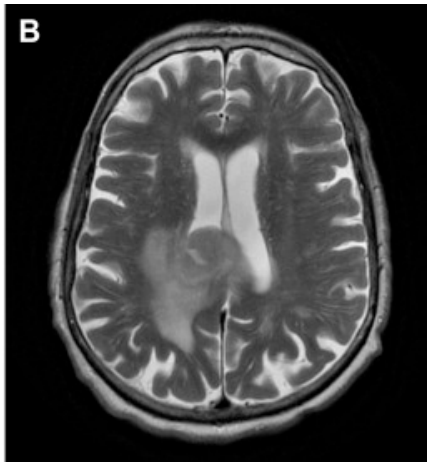
- **T1-MRI post-contrast with DWI** is diagnostic imaging modality of choice.
- **Stereotactic core-needle biopsy** is used for definitive diagnosis
  - Corticosteroids are necessary for the treatment of cerebral edema, but may confound diagnosis by temporarily decreasing size and altering histopathologic characteristics. Avoid prior to biopsy unless medically indicated.
  - **CSF studies** used for diagnostic measures if biopsy is not recommended.
- **Slit lamp exam** used to rule out vitreoretinal involvement with follow-up vitrectomy if suspected ocular involvement.
- **Spinal MRI** obtained if spinal symptoms are present
- **Labs**: CBC, CMP, serum LDH, Hep B and C, and HIV testing.
- **Whole-body FDG-PET and testicular US** with follow-up BMB if suspected systemic involvement (rare).
- **Staging**: there is no standard staging system for PCNSL. Initial prognosis dependent on IELSG/MSKCC scores.

Diagnostic Imaging

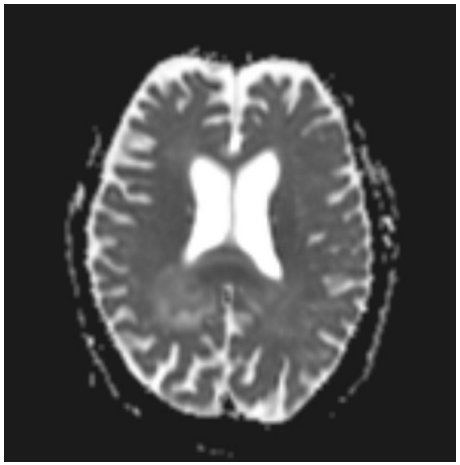
- **T1-post contrast with DWI**:
  - CNS lymphomas commonly periventricular.
  - High-grade tumors show hyper-intense homogenous enhancement while low-grade tumors show hypo-intense vs absent enhancement.
  - Diffusion restriction and mild-moderate edema present.
  - Macroscopic solitary lesion with potential microscopic multifocality, especially in immunocompromised patients.
  - Potential peripheral ring enhancement, especially in immunocompromised patients.



T1-post contrast MRI



T2-post contrast MRI


Diffusion weighted imaging

Prognosis

- Determined by IELSG or MSKCC scoring systems (seen right).
- At time of diagnosis, patients have average **5-year overall survival of 30%.** Following standard induction therapy, there is an 85% chance of tumor regression and increased OS (Grommes *et al*, 2018).
- Unfortunately, there is 50% relapse rate within 10-18 months following treatment. Relapsed or refractory PCNSL has poor prognosis with median survival of 2 months without treatment (Mendez *et al*, 2018).
- HIV-associated PCNSL before treatment has median OS 2-4 months and after treatment has median OS 1.5 years.

IELSG and MSKCC Scoring Systems

Variable	Favorable Feature (Value 0)	Unfavorable Feature (Value 1)
Age (years)	<60	>60
ECOG PS	0-1	>1
LDH serum level	Normal	Elevated
CSF protein level	Normal	Elevated
Involvement of deep regions of the CNS	No	Yes

MSKCC Prognostic Model for PCNSL [68]

Variable	Good Risk	Intermediate Risk	High Risk
Age	<50	≥50	≥50
ECOG PS		≥70	<70

PCNSL, primary central nervous system lymphoma; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, lactate dehydrogenase; CSF, cerebrospinal fluid; MSKCC, Memorial Sloan-Kettering Cancer Center.

IELSG 2-year OS	MSKCC median OS
Score 0-1 = 80%	Good risk = 8.5 yr
Score 2-3 = 48%	I.M. risk = 3.2 yr
Score 4-5 = 15%	High risk = 1.1 yr

Comparison of prognosis s/p induction therapy by IELSG vs MSKCC scoring systems (Grommes, 2018).

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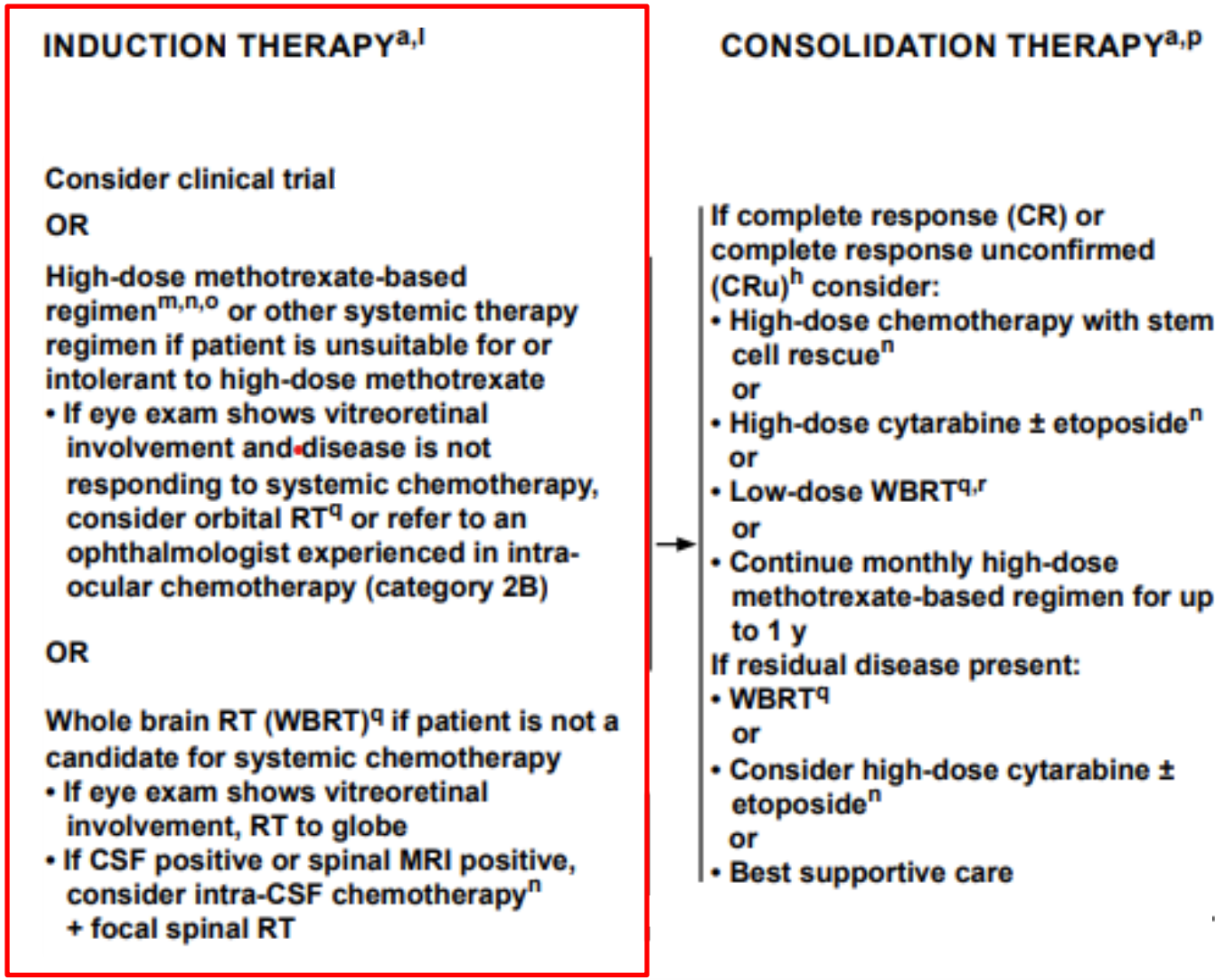

INDUCTION THERAPY[a,l]

Consider clinical trial

OR

High-dose methotrexate-based regimen[m,n,o] or other systemic therapy regimen if patient is unsuitable for or intolerant to high-dose methotrexate

- If eye exam shows vitreoretinal involvement and disease is not responding to systemic chemotherapy, consider orbital RT[q] or refer to an ophthalmologist experienced in intra-ocular chemotherapy (category 2B)

OR

Whole brain RT (WBRT)[q] if patient is not a candidate for systemic chemotherapy

- If eye exam shows vitreoretinal involvement, RT to globe
- If CSF positive or spinal MRI positive, consider intra-CSF chemotherapy[n] + focal spinal RT

CONSOLIDATION THERAPY[a,p]

If complete response (CR) or complete response unconfirmed (CRu)[h] consider:

- High-dose chemotherapy with stem cell rescue[n]

or

- High-dose cytarabine ± etoposide[n]

or

- Low-dose WBRT[q,r]

or

- Continue monthly high-dose methotrexate-based regimen for up to 1 y

If residual disease present:

- WBRT[q]

or

- Consider high-dose cytarabine ± etoposide[n]

or

- Best supportive care

Induction chemotherapy

- Standard chemotherapy agents for systemic DLBCL lack efficacy in PCNSL; **HD-methotrexate 3.5-8 g/m^2** is needed to cross BBB and achieve CSF cytotoxicity (Batchelor *et al*, 2003).
- Polychemotherapy proven more effective than MTX alone (Ferreri *et al,* 2017); regimen based on provider preference:
- **Common Induction Regimens:**
  1. MT-R = HD-MTX/rituximab/TMZ
  2. MATRiX = HD-MTX/rituximab/cytarabine/thiotepa
  3. R-MVP = HD-MTX/rituximab/vincristine/procarbazine
  4. R-MVBP = HD-MTX/rituximab/BCNU/teniposide/prednisone

- Vitreoretinal involvement can be treated with 1st line regimens +/- intra-ocular HD-MTX in persistent cases. RT may be used in refractory cases.
- HIV positive patients require ID consultation. Combination-ART should be considered in conjunction with induction chemotherapy.

IPCG Response Criteria Guidelines

	Complete Response (CR)	Uncomfirmed Complete Response (CR_u)	Partial Response (PR)	Progressive Disease (PD)
Gd+ MRI Imaging	No contrast enhancing disease	No contrast enhancing disease	≥ 50% reduction in enhancing lesion	> 25% increase in enhancing lesion or new lesion
Ocular/CSF exam	Normal/Negative	Normal/Negative	≥ 50% reduction in involvement with persistent malignant or suspicious cells	Recurrent or new disease
Steroid use	None ≥ 2 wk	Any	Irrelevant	Irrelevant

Abrey *et al, (*2005)

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or

- Continue monthly high-dose methotrexate-based regimen for up to 1 y

If residual disease present:

- WBRT[q]

or

- Consider high-dose cytarabine ± etoposide[n]

or

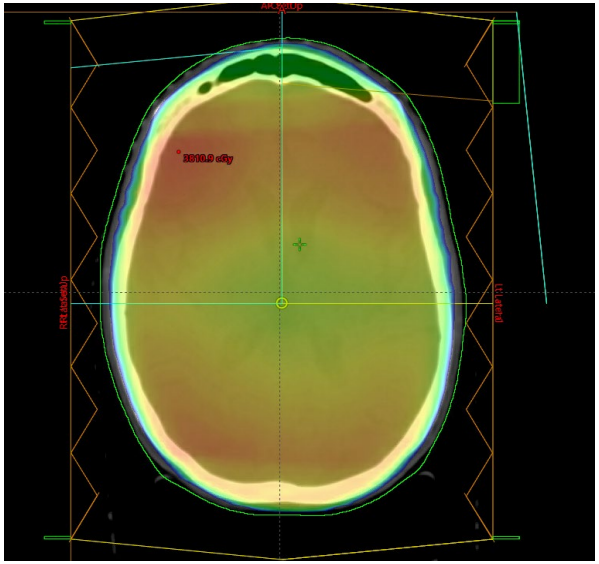
- Best supportive care

Consolidation Methods

- **Myeloablative HDC-ASCT for CR/CR_u:** preferred in young, otherwise healthy patients (Ferreri, *et al*, 2016).
  - HDC-ASCT is associated with PFS comparable to WBRT 36-45Gy consolidation without significant neurotoxicity **(PRECIS, IELSG32)**.
- **rdWBRT consolidation for CR/CR_u/PR:** 23.4 Gy/1.8 Gy per fraction +/- boost up to 45 Gy of areas without CR.
  - Excellent ORR and PFS with decreased neurotoxicity using rdWBRT in patients with CR **(MSKCC-01-146 and RTOG-1114)**. Now, rdWBRT is commonly used over WBRT in patients with CR who are **poor candidates for ASCT.**
- **Non-myeloablative HDC for CR/Cr_u/PR:** young or elderly patients (Chamberlain *et al,* 2013).
  - HD-etoposide/Ara-C shown to have OS/PFS comparable to historical WBRT controls without significant neurotoxicity **(CALG-50202).**
- **Maintenance chemotherapy for CR/Cr_u:** otherwise poor candidates for HDC or RT.
  - Agents: HD-MTX, rituximab, TMZ, procarbazine, lenalidomide, and ibrutinib.
  - Used to prolong PFS and QOL in more vulnerable patients.

Historical role of WBRT

- Historically, 40Gy WBRT + 20Gy boost to tumor site was used as definitive treatment but had high recurrence and median OS 12-18mo. **(RTOG-8315).**
- Discovery of induction HD-MTX as promising therapy when used in conjunction with consolidation 45Gy WBRT (median OS 30-60mo.) changed first line treatment to induction chemotherapy with WBRT consolidation. **(RTOG-9310).**
- Eventually, induction HD-MTX + consolidation 45Gy WBRT was found to increase PFS but not OS when compared to HD-MTX alone. Additionally, WBRT arm was found to have **increased risk of neurotoxicity**. **(G-PCNSL-SG-1).**



- **Current recommendation for WBRT:** HD-MTX based polychemotherapy is now first-line for induction therapy. Due to reduced risk of neurotoxicity, rdWBRT (24-36Gy) has replaced WBRT (45-60Gy) as consolidation regimen following successful response to chemotherapy.

Chemo +/- Consolidation 45Gy WBRT: G-PCNSL-SG-1

- 2010 Multicenter phase III study to assess efficacy of HD-MTX +/- adjuvant WBRT therapy in immunocompetent PCNSL patients.
- *Eligibility*
  - Eligible: > 18yrs, ≤ 2 weeks from confirmation of PCNSL, KPS ECOG ≤ 3
  - Ineligible: prior PCNSL therapy or cranial RT, pre-existing immunodeficiency or other primary malignancies, immunosuppression or active infection.
- **Arm 1**: HD-MTX with WBRT 45 Gy/1.5 Gy per fraction.
- **Arm 2**: HD-MTX without WBRT.
- **Primary outcome:** OS within 3 years
- **Secondary outcome:** PFS within 3 years
- **Results**: PFS shown superior with WBRT, but OS was shown to have no difference. WBRT had increased risk of neurotoxicity.
- **Disclaimer:** trial had several methodological flaws; non-inferiority margin not met.

CR Consolidation with rdWBRT:

MSKCC-01-146

- 2013 multicenter phase II study assessed efficacy of R-MVP induction with consolidation rdWBRT + adjuvant cytarabine in immunocompetent PCNSL patients.
- *Eligibility*
  - Eligible: confirmed untreated immunocompetent PCNSL.
  - Ineligible: prior PCNSL treatment, pre-existing immunodeficiency, other primary malignancies, or systemic PCNSL involvement.
- **Arm 1**: R-MVP chemotherapy → CR received rdWBRT 23.4 Gy/ 1.8 Gy per fraction + cytarabine; PR received WBRT + cytarabine.
- **Primary outcome:** adverse effects; PFS
- **Results**: induction chemotherapy with adjuvant rdWBRT associated with high response rate and long-term disease control with **minimal neurotoxicity**.

CR Consolidation with rdWBRT:

RTOG-1114

- 2020 multicenter randomized phase II study assesses efficacy of induction polychemotherapy with adjuvant rdWBRT for immunocompetent PCNSL patients.
- *Eligibility:*
  - Eligible: confirmed untreated immunocompetent PCNSL.
  - Ineligible: prior PCNSL treatment, pre-existing immunodeficiency, other primary malignancies, or systemic PCNSL involvement.
- **Arm 1:** Induction chemotherapy without rdWBRT.
- **Arm 2:** Induction chemotherapy with rdWBRT, 23.4 Gy/1.8 Gy per fraction.
- **Primary Outcome:** PFS
- **Secondary Outcome:** OS, PR vs CR, quality of Life (EORTC), neurocognitive function.
- **Results:** addition of rdWBRT improved PFS in newly diagnosed PCNSL without significant increase in neurotoxicity.

RTOG
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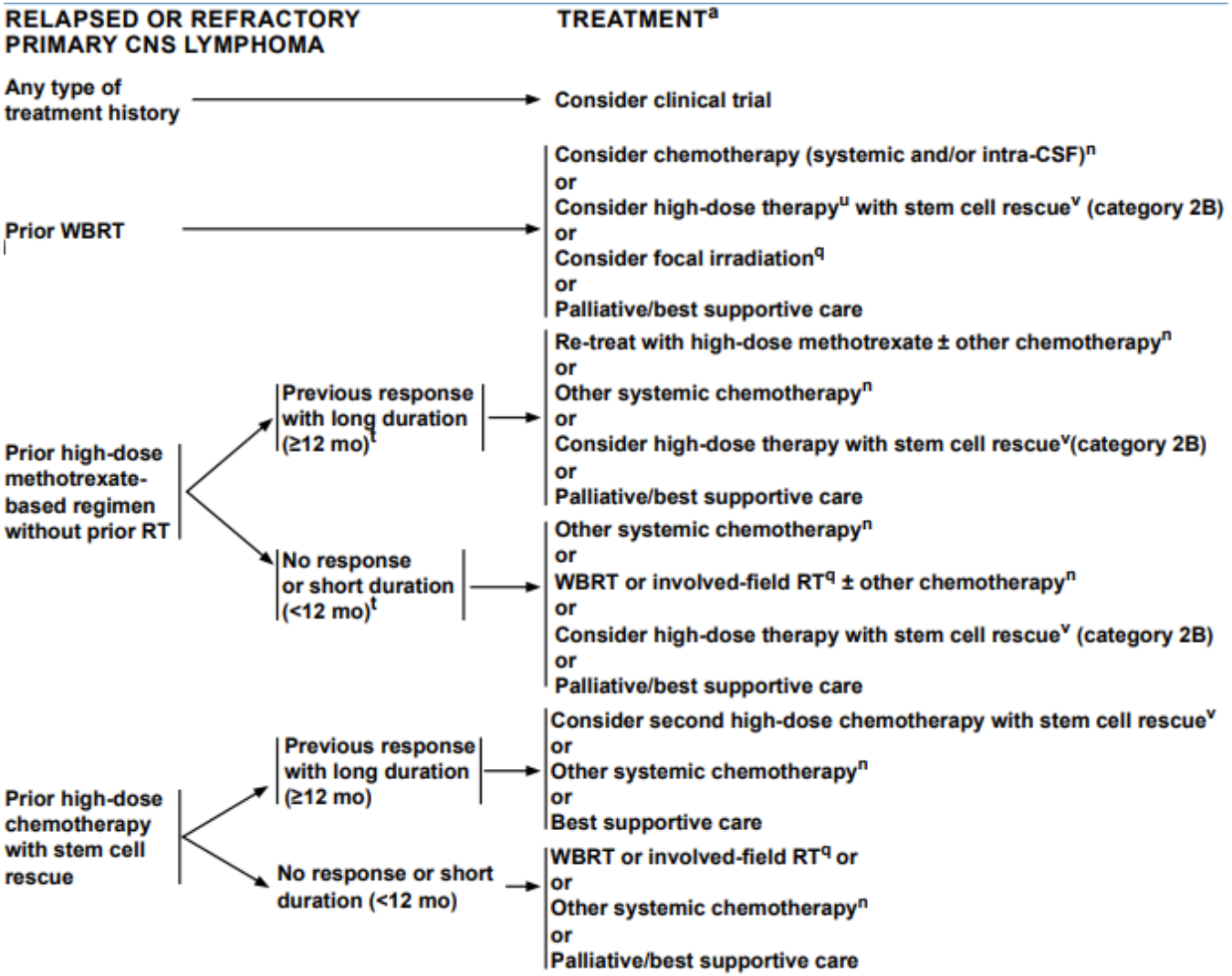
Maintenance

- **Maintenance Imaging**
  - Brain T1-MRI post contrast with DWI.
  - Every 3 months until 2 years → every 6 months until 5 years → annually indefinitely.
- **Initial spinal involvement:**
  - Spinal MRIs with concurrent brain MRIs and CSF sampling when clinically indicated.
- **Initial ocular involvement**:
  - Concurrent ophthalmologic follow-up as clinically indicated.

Salvage Therapy



Salvage Therapy

- **Re-challenging with HD-MTX-based therapy** is effective in patients who previously achieved CR for >12 mo. with HD-MTX-based chemotherapy.
  - **HDC-ASCT** remains an option in younger patients with previous response to HDC-ASCT >12 mo. and successful response to salvage chemotherapy.
- **Clinical Trials** are promising agents, considered in patients who cannot tolerate HD-MTX-based chemotherapy. TMZ especially shown to be effective (R-MT regimen).
  - Ongoing trials: TMZ, pemetrexed, topotecan, rituximab
- **Immunotherapy and novel targeted therapies** are promising and most likely to be used in combination with current standard therapies. Considered in patients who cannot tolerate HD-MTX-based regimens.
  - Available agents: nivolumab, ibrutinib, lenalidomide

Salvage WBRT

- WBRT is used as last-resort in patients who are radiation-naiive with initial CR <12mo. where **systemic therapy is not a viable option**.
- 24-36 Gy/1.8 Gy per fraction + focal boost of gross disease up to 45 Gy.
  - Refractory or recurrent disease treated with WBRT is associated with significant neurotoxicity and short duration of response with PFS of 9-10 mo. and OS 10-16 mo. This is improved from baseline 2-month survival with no treatment (Nguyen *et al,* 2005).
  - For patients >60 years, consider WBRT only for palliative measures.

Conclusions

- PCNSL occurs more commonly in immunocompromised individuals with a growing incidence in the elderly.
- T1-MRI post-contrast is imaging modality of choice. Stereotactic biopsy or CSF studies are diagnostic.
- Standard induction consists of HD-MTX-based polychemotherapy or monotherapy depending on age and performance status.
- Consider treatment intensification with HDC-ASCT consolidation in young patients with good performance status.
  - Consolidation therapy with rdWBRT is considered in patients who are ineligible for systemic therapy.
- Salvage therapy with chemotherapy or WBRT, may consider HDC-ASCT in young patients with good performance status.

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