On Point in Primary CNS Lymphoma

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Abstract

Primary CNS lymphoma (PCNSL) is an aggressive brain tumor that represents a significant challenge both to elucidate its biological pathogenesis as well as to develop definitive precision medicines with minimal collateral toxicity. We highlight the key issues in diagnosis and treatment and focus on emerging technologies, current options among consolidation strategies, and biological agents. We anticipate that further development of molecular diagnostics and molecular imaging approaches that elucidate minimal residual disease in brain parenchyma, leptomeninges, intraocular compartments and even bone marrow will greatly impact the delivery and timing of cytotoxic and biological therapies. Implementation of these approaches is likely essential to clarify ongoing discrepancies in the interpretation of clinical trial results that currently are based on relatively unrefined definitions of response. While the results of early phase investigations involving ibrutinib and the IMiD agents, lenalidomide, pomalidomide, as well as avadomide, strongly support the hypothesis that the B-cell receptor (BCR) pathway, involving MYD88 and CD79B and NF-kB activation, is critical to the pathogenesis of PCNSL, much work is needed to elucidate mechanisms of resistance. Similarly, development of strategies to overcome immunosuppressive mechanisms that are upregulated in the tumor microenvironment is a high priority. Finally, ongoing evidence supports the hypothesis that the blood-brain barrier represents

a significant impediment to efficient brain tumor penetration of novel therapeutic agents and innovative strategies of drug delivery remain essential to further improve outcomes.

Introduction

We provide perspective and commentary on the landscape of significant issues in the clinical practice and research of PCNSL.

Disease Assessment and Minimal Residual Disease

While novel strategies to detect minimal residual disease (MRD) are widely implemented in hematologic malignancies,[1] the application of molecular testing strategies to assess MRD are not yet routine in PCNSL. In PCNSL there remains a significant gap in the rational implementation of therapy that is based on recognition of minimal disease status, both with respect to initial staging as well as the assessment of response and duration of treatment with high-dose methotrexate-based therapies.

The first application of polymerase chain reaction (PCR)-based molecular detection to disease assessment in PCNSL was the demonstration of subclinical systemic disease in patients via detection of identical rearranged lymphoma-associated immunoglobulin heavy chain genes (*IgH* gene PCR) in bone marrow, peripheral blood specimens and tumors in a small subset of

patients (8.3%).[2] These results suggest that a significant fraction of PCNSL patients staged by standard assays actually have occult systemic disease that may not be adequately treated by methotrexate-based protocols that are optimized for PCNSL. To date, no study has rigorously considered the potential relationship between the presence of subclinical systemic disease and early disease progression with methotrexate-based induction in PCNSL. Based on our own experience in bone marrow staging of PCNSL, it is plausible that systemic FDG-PET is inadequate in detection of occult disease detected by molecular assays such as IgH gene PCR or even flow-cytometry.

A major challenge in the management of patients with PCNSL is in the radiographic assessment of response and minimal residual disease in brain. The standard radiographic metric for response assessment is the 1990 MacDonald criteria, based on dimensions of contrast enhancement on T-1 based magnetic resonance imaging (MRI) and extrapolated from studies of malignant glioma.[3] While useful as a surrogate for complete response (CR), this metric has important limitations in PCNSL. (Figure 1)

Notably, it is established that while 50% of PCNSL tumors in immunocompetent patients are recognized at baseline as a solitary enhancing lesion on T1-weighted MRI, ~ 25% of lesions present with a spatially distinct non-enhancing hyperintense focus identified on T2/FLAIR (fluid attenuated inversion recovery) weighted imaging, [4] This is consistent with lymphomatous dissemination in the brain in the absence of contrast enhancement on MRI.

Importantly, while T2/FLAIR sequences can detect subclinical, non-enhancing dissemination of CNS lymphoma, confounding MRI abnormalities involving white matter are

elicited by chemotherapy agents including HD-MTX, 5-FU, as well as brain irradiation and the effects of normal aging.

There is strong interest in development of novel, advanced imaging approaches to non-invasively detect and provide prognostic insight as well as MRD detection. One approach is diffusion-weighted imaging, which measures restricted water diffusion in hypercellular tumors such as PCNSL, resulting in hyperintensity on MRI. Foci of restricted diffusion may discriminate residual CNS lymphoma from benign processes, and very low diffusion coefficients have been associated with high-risk, aggressive CNS lymphoma.[5-8] Restricted diffusion on MRI distinguish PCNSL from less cellular tumors such as malignant gliomas. Other advanced imaging approaches in routine clinical use include magnetic resonance spectroscopy and PET, each of which are capable of detecting tumor-associated Warburg metabolism.[9]

While PCNSL are often [^{18}F]FDG-avid, PET imaging for PCNSL has limitations: high FDG uptake occurs in normal brain and is confounded by macrophage infiltration in inflammatory and treatment responses.[9, 10] Moreover, recent studies of PET in PCNSL demonstrated that interim [^{18}F]FDG PET failed to predict overall survival with standard therapies,[11, 12] and the largest study suggested that the low specificity and frequent false negatives of interim [^{18}F]FDG PET limits utility in PCNSL compared to systemic DLBCL.[11] These studies suggest that FDG PET may have limitations as a sole modality for prognostic and MRD evaluation in PCNSL. Preclinical studies support the potential of hyperpolarized [1-^{13}C] pyruvate-based MRI to detect highly infiltrative PCNSL and to detect response to NF-kB targeting agents.[13]

Tumor Microenvironment in Primary CNS Lymphoma

In parallel there has been progress in development of biologically relevant biomarkers from within cerebrospinal fluid (CSF), a component of the tumor microenvironment in PCNSL.[14] CXCL-13, a B-lymphocyte chemoattractant, stimulates chemotaxis of large B-cell lymphoma cells isolated from brain lesions, and elevated CXCL-13 correlates with adverse prognosis, supporting its role as a pro-survival factor in PCNSL. In addition, determination of CSF concentrations of both CXCL-13 and the immunosuppressive Th2 cytokine IL-10[15] facilitates diagnosis of PCNSL, as bivariate expression of each molecule has diagnostic sensitivity for PCNSL that is greater than two-fold higher compared to flow-cytometry or cytology. In a multicenter investigation, the positive predictive value of elevation of both IL-10 and CXCL-13 in CSF was 95% in identification of untreated PCNSL.[16] CSF IL-10 also has strong potential as an early pharmacodynamic biomarker of response to lenalidomide.[17]

Circulating extracellular nucleic acids in CSF, including both microRNAs such as miR-21 well as circulating tumor DNA may have utility as clinical biomarkers of MRD status in PCNSL.[18, 19]

Metabolomic profiling of CSF recently yielded identification of candidate mediators of CNS lymphoma pathogenesis. Notably, multiple immunosuppressive metabolites were discovered to be upregulated in CSF from CNS lymphoma compared to controls, including lactic acid,[20] 5-methylthioadenosine,[21] dimethylarginine[22] as well as kynurenine, a metabolite of tryptophan that is associated with T-cell inhibition via the indoleamine-2,3 dioxygenase (IDO) pathway.[23-25] Marked upregulation of IDO1 transcripts was demonstrated in diagnostic specimens of PCNSL compared to non-neoplastic brain and IDO1 expression was localized to both lymphoma and tumor-associated macrophages. Changes in kynurenine/tryptophan ratios, reflective of IDO

activity, correlate with progression and/or response to lenalidomide. These data suggest that multiple immunosuppressive mechanisms are upregulated in CSF, correlate with disease activity, and represent pharmacologic targets to enhance innate and adaptive immunity,[26] as well as biomarkers of response and potentially of MRD.[17]

Consolidation Strategies in Primary CNS Lymphoma

The heightened efficacy of dose-intensive methotrexate in overcoming the blood-brain barrier to cytoreduce CNS lymphomas was first appreciated by Skarin, Canellos and colleagues.[27] Given the inevitable resistance to methotrexate monotherapy,[28] a combined modality approach was pioneered by DeAngelis at Memorial Sloan-Kettering (MSKCC), who later began to systematically define the devastating complications of whole brain irradiation (WBRT) in PCNSL.[29, 30] A dominant question during the past five years of research in PCNSL has been determination of the optimal consolidation strategy: WBRT vs. dose-intensive chemotherapeutic consolidation, and among chemotherapeutic strategies: myeloablative vs. non-myeloablative therapy.

A key finding of the RTOG-93-10 phase II trial evaluating the MSKCC regimen involving consolidative WBRT in PCNSL, was the determination that > 15% of patients exhibited severe delayed neurotoxicity within one year: a syndrome of irreversible memory deficits, apathy, problems with concentration, urinary incontinence and gait disturbance[31] (Figure 2). Given concerns over neurotoxicity, recently two randomized multicenter European studies have compared outcomes with WBRT vs. myeloablative therapy and autologous stem cell transplantation (ASCT) in PCNSL: the IELSG32 trial and the PRECIS study.

The French PRECIS trial enrolled 140 PCNSL patients, age ≤ 60 years, who were treated with induction high-dose methotrexate, rituximab, BCNU, prednisone and depocyt. Responding patients were randomized to consolidation with either whole brain irradiation (40 Gy) or myeloablative therapy with an aggressive preparative regimen consisting of thiotepa, bulsulfan and cyclophosphamide (TBC regimen). As described in their 2019 publication, with median follow-up of 33.5 months, event-free survival (EFS) in the ASCT arm was significantly longer than in the WBRT arm. ($P<0.03$) However a stable plateau in EFS by Kaplan-Meier analysis was not achieved beyond two years in the chemotherapy-arm. The TBC regimen was associated with an 11% rate of treatment-related mortality, in this study [32] as well as in a single center phase II investigation. [33]

In parallel, Ferreri and colleagues successfully executed a highly complex multicenter trial with two stages of randomization that addressed several questions during induction and consolidation phases.[34, 35] Two hundred twenty-seven patients from five countries, age up to 70 years, were enrolled and one hundred eighteen patients proceeded to the second randomization stage that compared myeloablative consolidation with a preparative regimen consisting of carmustine plus thiotepa[36] vs. whole brain irradiation (36 Gy plus 9 Gy boost to tumor bed). In contrast to the PRECIS study, there was no difference in two-year progression-free survival (PFS) between the two arms, with median follow-up of 40 months. Notably, the treatment-related toxicity with ASCT using the carmustine/thiotepa preparative regimen was only 3.4%, but there were five late deaths, and neither arm showed evidence for a stable plateau in disease progression over time.

An important conclusion, shared by both studies, is that neurocognitive endpoints, analyzed in great detail, showed improved outcomes in patients treated with dose-intensive chemotherapy compared to those that received WBRT. In each study at two-year follow-up, patients treated with ASCT showed improvements in executive function, memory and quality of life compared to patients treated with WBRT, in whom these functions showed time-dependent declines.

A key question raised in the comparison of these two trials is prompted by the differences in outcomes: specifically, why was survival better with transplant than WBRT in the PRECIS study but not in the IELSG32 trial? One potential explanation is that the quality of response to induction therapies may markedly differ between the two trials. It is possible that the comparison of two consolidation regimens in patients with potentially markedly heterogenous burdens of MRD may be unbalanced between arms and introduce an unanticipated confounding variable. The potential significance of this variable, albeit theoretical, is heightened given that patients with both complete and partial responses as well as patients with stable disease, proceeded to consolidation. The heterogeneity of induction regimens within the IELSG32 trial may greatly contribute to this issue, as this trial used three different induction regimens with markedly distinct efficacies in inducing complete responses: (1) methotrexate plus cytarabine (rate of CR 23%), (2) rituximab plus methotrexate and cytarabine (rate of CR 30%) and (3) thiotepa plus rituximab, methotrexate and cytarabine (the MATRix regimen (rate of CR 49%).

Given the inadequacies of assessing CR status using standard MRI criteria in PCNSL,[37] we hypothesize that the application of novel imaging approaches and more sensitive molecular biomarkers, in the brain, CSF and potentially bone marrow microenvironments, to assess depth

of response to induction and MRD, is a key area to be developed in future investigations that will lead to improvements in the selection, timing and outcomes with chemotherapy-based consolidation.

The Alliance for Clinical Trials Cooperative Group in the United States is conducting a study that compares outcomes in 113 PCNSL patients (age up to 75 years) who received a uniform induction regimen consisting of methotrexate plus temozolomide and rituximab (MT-R) followed by high-dose cytarabine and then proceeded to two distinct consolidation regimens: myeloablative with carmustine/thiotepa-based preparative regimen and non-myeloablative therapy with dose-intensive infusional etoposide plus cytarabine (Alliance 51101). The rationale for this trial is based on results of CALGB 50202 which first demonstrated the feasibility of high-dose chemotherapy-based consolidation in a multicenter study in PCNSL and which yielded median PFS of 2.4 years with etoposide/cytarabine consolidation, with a median follow-up of 4.9 years. Notably, the PFS curve stabilized after two years, suggesting that a major fraction of patients achieved durable remissions and cure. In CALGB 50202, only patients who achieved complete response to induction therapy proceeded to the consolidation phase, further supporting the possibility that depth of response to induction therapy may be an under-appreciated factor that is requisite to achieve long-term remission in this disease. Results of the CALGB 50202 regimen, developed at UCSF, were confirmed in community practice in a French study, described by Birsen *et al.,* in which there was no treatment-related mortality associated with dose-intensive consolidation with etoposide/cytarabine.

While WBRT-based consolidation using doses of $\geq$36 Gy have reproducibly been demonstrated to yield deleterious neurocognitive outcomes compared to dose-intensive

chemotherapy in PCNSL, investigators at MSKCC also evaluated low-dose WBRT (23.4 Gy) as consolidation. Favorable PFS and neurocognitive outcomes were described in a phase II analysis published in 2013.[38] However this study had notable limitations: (1) the studied cohort was younger than the typical PCNSL population: only three patients were older than 60 years; (2) significant neurocognitive deficits with similar doses administered as prophylactic cranial irradiation have been described in lung cancer patients,[39] raising a concern about reproducibility of results; (3) there is significant potential of radiation-induced secondary brain tumors among survivors, including glioblastoma; (4) the option of repeat irradiation to the brain may not be feasible as salvage, should there be disease progressions after initial low-dose irradiation consolidation.

Biological and Targeted Therapies in Primary CNS Lymphoma

There is universal agreement that rituximab has a positive impact on event-free, progression-free and overall survival in diffuse large B-cell lymphoma outside the CNS. The addition of rituximab to chemotherapy reduces risk of death by 10% after 6 years with an absolute reduction in risk for progression by 16% (HR = 0.48).[40] By contrast, a recent meta-analysis of two randomized controlled trials involving 343 subjects that evaluated the impact of rituximab in combination with high-dose methotrexate in PCNSL concluded that the pooled hazard ratio for overall survival showed no statistically significant benefit with the addition of rituximab. The meta-analysis did however detect evidence for improvement in PFS, although because of apparent lack of precision in estimates and potential bias in determination of PFS, it was concluded that even a potential benefit of rituximab in terms of PFS could not be firmly established.[41]

The blood-brain barrier may significantly limit tumor penetration of large molecules such as intravenously-administered rituximab into PCNSL, compromising its efficacy in highly infiltrative components of disease.[42] It has been demonstrated that concentrations of rituximab in CSF are approximately 0.1% of serum levels associated with therapeutic activity in patients with systemic non-Hodgkin lymphoma. [43] For this reason, several early phase studies conducted at UCSF, MSKCC and Harvard have evaluated the safety and activity of rituximab administered by the intraventricular route into CSF, demonstrating feasibility and significant activity of rituximab both as monotherapy and in combination with intraventricular methotrexate; responses were observed in CSF, deep brain and intraocular lymphomas, including in patients whose CNS lymphomas were resistant to rituximab administered by the standard intravenous route.[44, 45] This route of administration of rituximab plus methotrexate may have particular efficacy in the cytoreduction of refractory leptomeningeal lymphomas. A pharmacokinetic model supports the possibility of deep brain penetration of rituximab administered via the intraventricular route, as a means to overcome the blood-brain barrier.[46]

Genetic evidence strongly indicates that PCNSL are dependent on pro-survival signals regulated by NF-kB, with enrichment of mutations involving the B-cell receptor (BCR) pathway, in particular MYD88 and CD79B.[47, 48] Early phase investigations of ibrutinib, an oral inhibitor of Bruton's tyrosine kinase (BTK), demonstrated significant activity as monotherapy in relapsed PCNSL, with a median PFS estimate of 4.6 months.[49] Furthermore, combinations of ibrutinib with high-dose methotrexate [18] and an experimental regimen, dose-adjusted-TEDDi-R, (temozolomide, etoposide, liposomal doxorubicin, dexamethasone and rituximab), have been shown to have promising activity. A concerning serious toxicity detected in many studies involving

ibrutinib in PCNSL is the development of invasive aspergillosis within brain and/or lungs of patients, with an incidence of 39% in the phase I TEDDi-R study.[50]

The risk of aspergillosis associated with ibrutinib may be a consequence of the antagonism of wild type BTK in innate immune cells that control Aspergillus infection. Toll like receptors (e.g. TLR 2, 4 and 9) engaged in response to fungal spores, signal through BTK in myeloid cells to induce TNF-α, which contributes to the recruitment of neutrophils.[47] While prolonged administration of glucocorticoids or other immunosuppressive mechanisms in PCNSL may be synergistic with ibrutinib in potentiating risk of Aspergillosis infection, it is now recognized that patients with chronic systemic lymphoproliferative disorders in general who are treated with ibrutinib exhibit increased risk of developing invasive aspergillosis even in the absence of neutropenia or glucocorticoid treatment.[51]

Notably, voriconazole, active in invasive aspergillosis, strongly induces CYP4503A4, and may complicate dosing of ibrutinib, a CYP4503A4 substrate. Isavuconazole, a related triazole with efficacy against aspergillosis and mild-to-moderate inducer of cytochrome P4503A4, was recently recognized to have potential compatibility with ibrutinib. [52] Investigators at the National Cancer Institute (NCI) are investigating safety, pharmacokinetics and efficacy of isavuconazole plus ibrutinib, to prevent aspergillosis, and as a component of TEDDi-R in PCNSL.

In parallel, several investigations of immunomodulatory (IMiD) agents have been demonstrated to be active in relapsed CNS lymphomas. Dose-dependent CSF penetration of lenalidomide has been demonstrated in a phase I trial that also reported activity of this IMiD, alone and in combination with intravenous and intraventricular rituximab.[17] Phase II studies of lenalidomide plus intravenous rituximab and pomalidomide plus dexamethasone also reported

significant activity.[53, 54] In addition, encouraging evidence for activity of lenalidomide as maintenance, after salvage in highly refractory patients, or in first remission in patients age > 70 has been described.[55, 56] A recent investigation of the novel cereblon modulator, avadomide (CC-122),[57] performed in part at UCSF, provided evidence for activity of this agent as monotherapy and in combination with dexamethasone in relapsed PCNSL. (Figure 3).

Other promising strategies include mTOR inhibition[58] as well as T-cell checkpoint blockade,[59, 60] particularly given the evidence for genetic upregulation of PDL1 via 9p24 copy number gain and the potential adverse prognostic significance of PD1 and PDL1 expression in PCNSL.[61, 62] CAR T-cell strategies also have significant potential, given emerging data that demonstrate activity in small lesions of secondary CNS lymphoma.[63]

Given the potential synergy in targeting immune as well as NF-kB driven pathways,[64] there is significant interest in combinatorial strategies to augment response proportions and minimize MRD before consolidation. Combination lenalidomide plus ibrutinib plus rituximab represents a promising approach in relapsed DLBCL including PCNSL, and the combination of checkpoint inhibitor plus ibrutinib represents another highly rational strategy. The combination of lenalidomide plus nivolumab with the induction backbone of methotrexate/rituximab (Nivo-MR2) is in development as a phase I multicenter trial in the U.S. The concept, approved by NCI/CTEP, will also investigate lenalidomide and nivolumab as a maintenance program in lieu of WBRT or dose-intensive chemotherapeutic consolidation. Quality of life studies are important to signal the complete picture of benefits and toxicities of biological-based strategies as an alternative to genotoxic consolidation.

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Ethical Statement: Retrospective analysis of patients with CNS lymphoma at UCSF was done in accordance with an IRB-approved protocol. Patients treated on the phase I trial involving avadomide (CC-122) signed informed consent in accordance with an IRB-approved protocol and the Declaration of Helsinki.

Figure Legends

Figure 1. Incomplete Resolution of Contrast Enhancement after Induction Therapy in PCNSL. A) A 65 year-old women presented on MRI with large enhancing and infiltrative masses in the left frontal lobe, crossing midline and with a right interior parietal lobule with marked mass effect resulting in sulcal effacement and nearly 1 cm rightward midline shift. B) After eight cycles of methotrexate-based therapy in combination with temozolomide plus rituximab (MT-R) there was marked resolution of mass effect and enhancing infiltrating masses. However, a residual focus of enhancement persisted within a focus of cystic encephalomalacia in the left medial orbital frontal gyrus and gyrus rectus, concerning for persistent disease. There were no foci of reduced diffusion to suggest progressive CNS lymphoma. This study illustrates one of the important limitations of conventional MRI-based evaluation of response in PCNSL: it is unclear whether residual enhancement reflects active lymphoma after an aggressive course of methotrexate-based induction, or whether the remaining enhancement is a consequence of incomplete repair of areas of disrupted blood-brain barrier, within a dead or dying tumor bed.

Figure 2. Treatment-Related Neurotoxicity: Contrasting Brain MRI's of Patients with CNS Lymphoma after WBRT vs. after High-Dose Chemotherapy and Autologous Stem Cell Transplant. MRI on the left is from a 52 year-old female patient diagnosed with CNS lymphoma with concomitant minimal bone marrow involvement who was treated with methotrexate plus R-CHOP (rituximab and cyclophosphamide, doxorubicin and vincristine) chemotherapy; because of primary refractory disease, the patient was then treated with lenalidomide followed by whole brain irradiation. The MRI on the right is from a 64 year-old female patient also diagnosed with CNS lymphoma and concomitant minimal bone marrow involvement who was also treated with methotrexate plus R-CHOP followed by consolidative myeloablative therapy with carmustine/thiotepa and autologous stem cell transplant, followed by one year of lenalidomide maintenance. The brain MRI from the patient treated with WBRT demonstrates far greater

volume loss and white matter disease compared to the brain MRI of the patient treated with dose-intensive consolidation chemotherapy. The patient on the left exhibits the archetypical late manifestations of WBRT: encephalopathy, memory deficits, apathy, decreased concentration, urinary incontinence and gait instability. She requires full-time custodial care. The patient on the right exhibits a normal performance status without neurologic deficits.

Figure 3. Response to the Novel Cereblon Modulator Avadomide (CC-122) in Methotrexate-Resistant PCNSL. Restaging after three months of treatment with CC-122 (4 mg/day) resulted in time-dependent regression of tumor-associated contrast enhancement on axial (upper panels) and coronal (lower panels) on T1 sequences of brain MRI. Left panel: baseline, pre-CC-122; middle panel, after two months of CC-122 therapy; right panel, after three months of CC-122 therapy.

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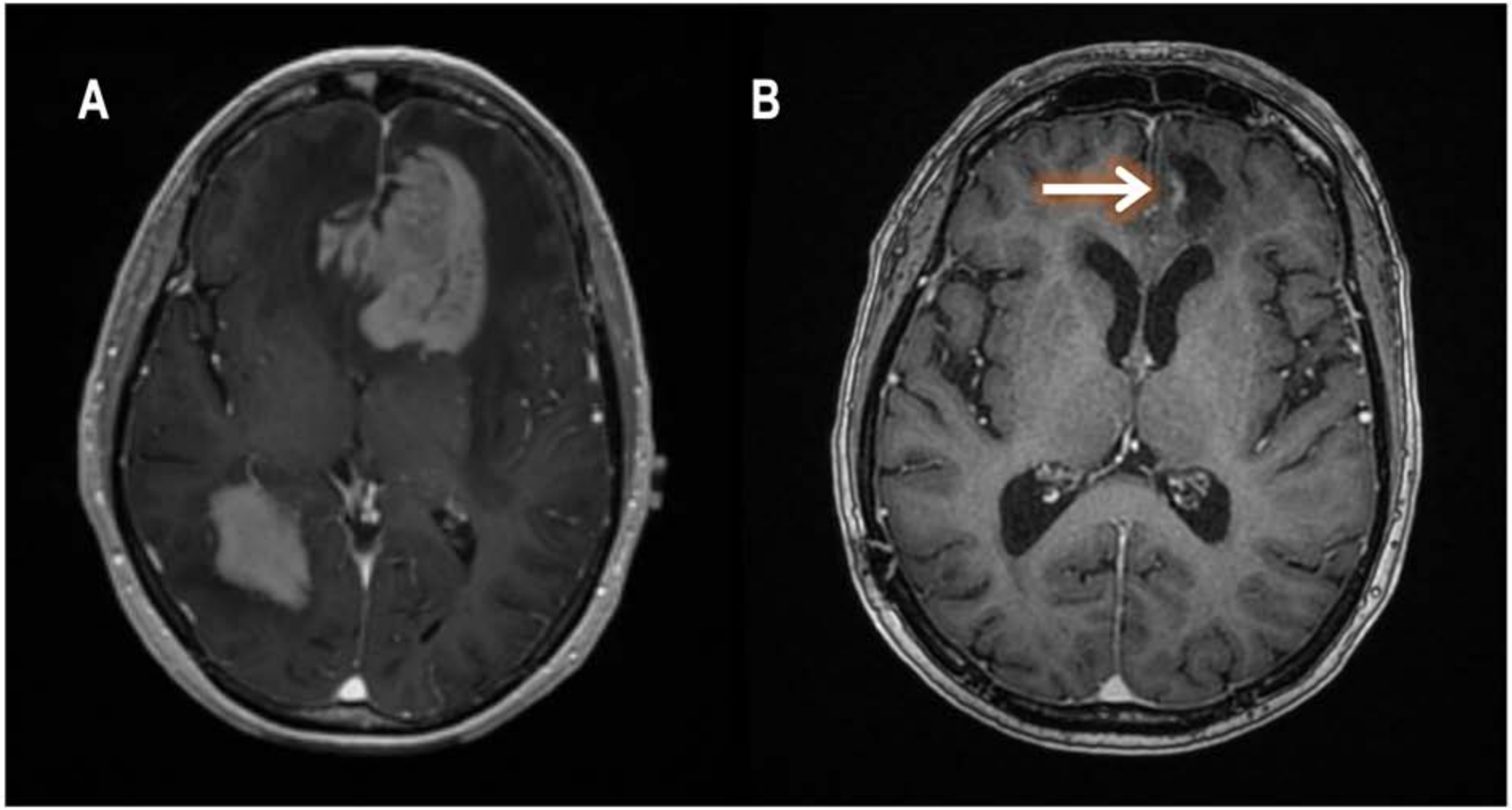
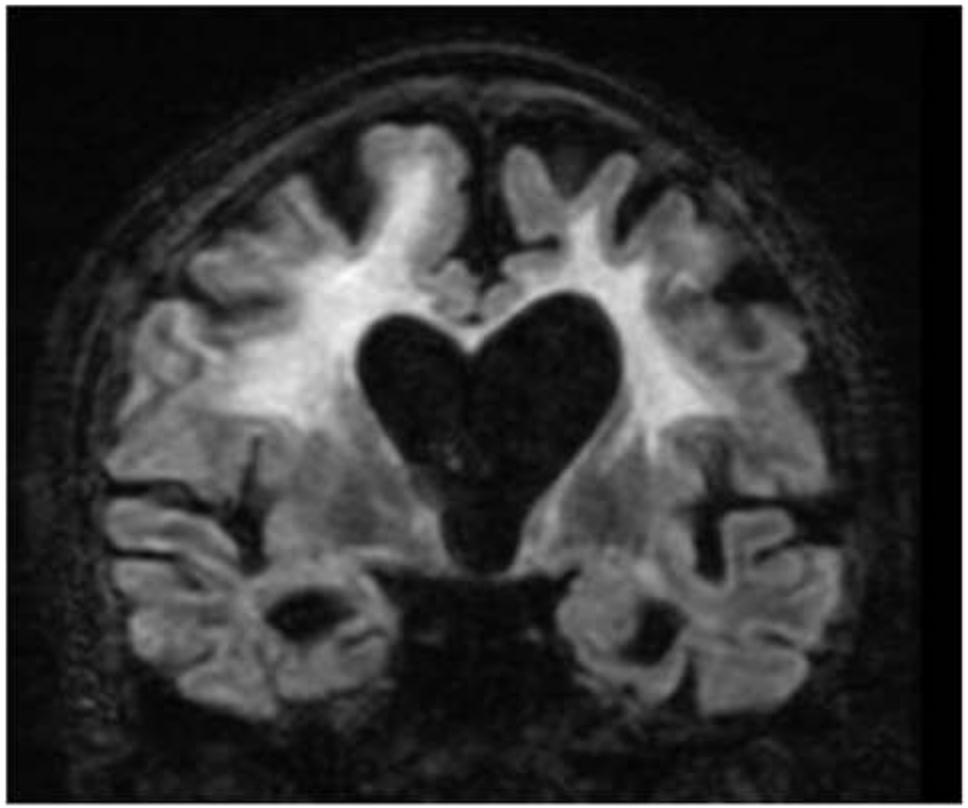
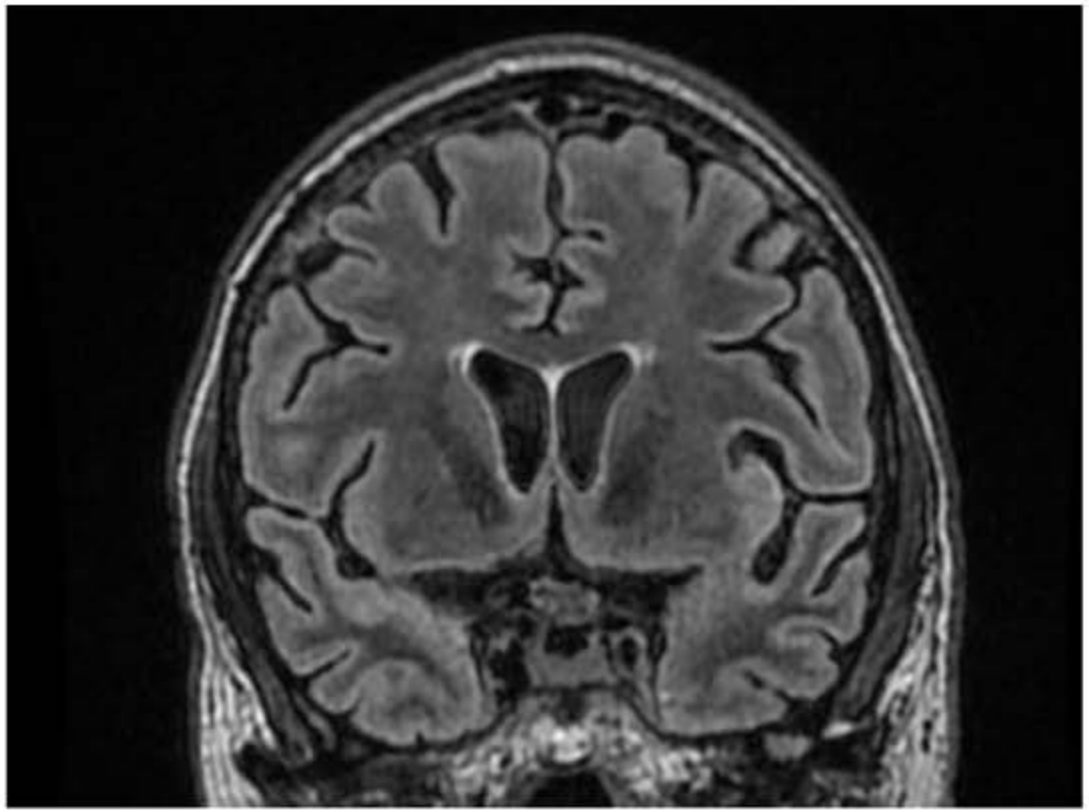




Age 52
Whole Brain Irradiation



Age 64
High-Dose Chemotherapy