Rituximab, methotrexate, procarbazine and vincristine followed by high-dose chemotherapy with autologous stem-cell rescue in newly -diagnosed primary CNS lymphoma (PCNSL)

THERAPEUTIC/DIAGNOSTIC PROTOCOL

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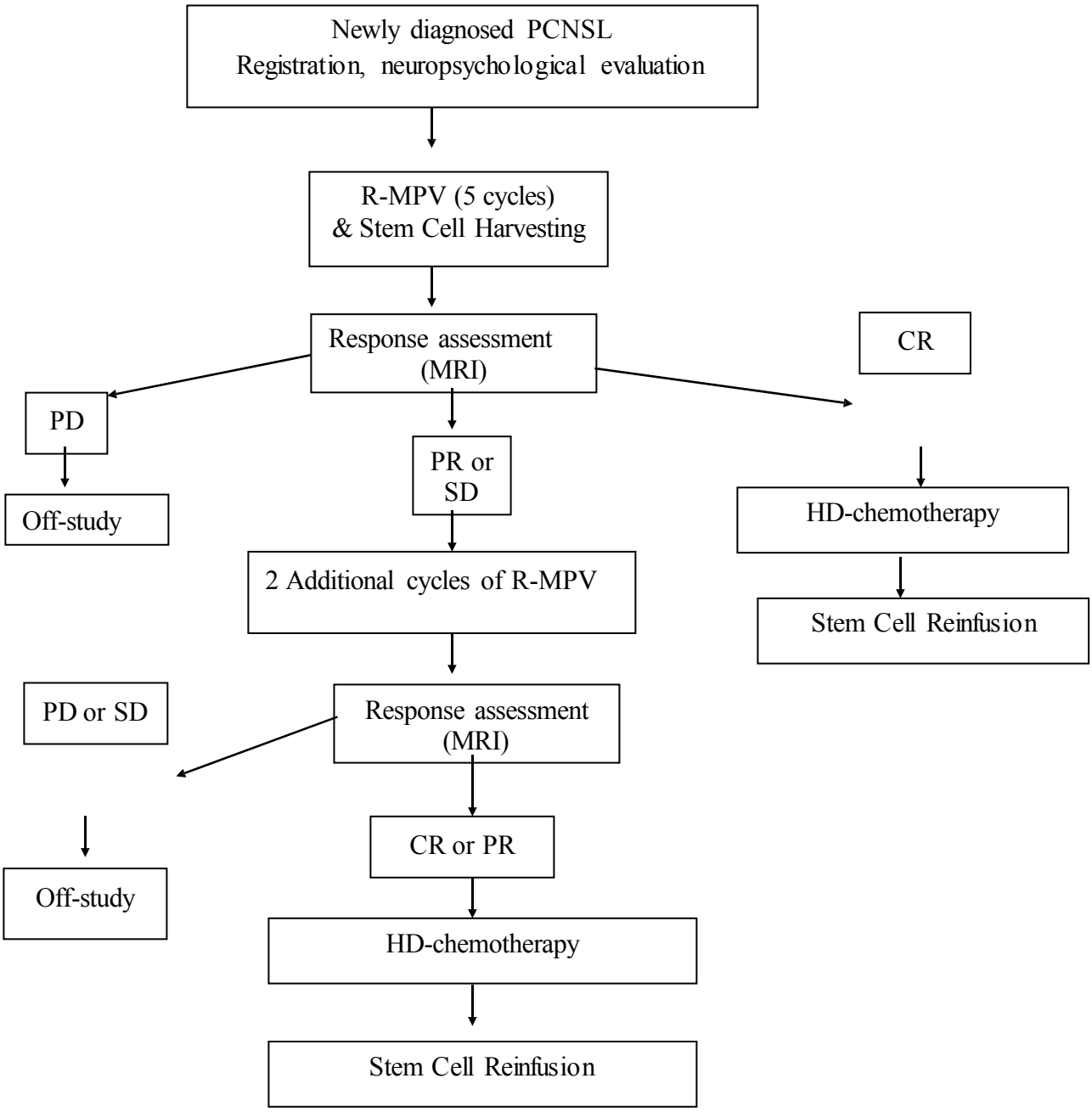
PROTOCOL SUMMARY AND/OR SCHEMA



2.1 OBJECTIVES AND SCIENTIFIC AIMS

2.1- Primary objective: to evaluate the safety and efficacy of the use of R-MPV followed by high-dose chemotherapy using thiotepa, cyclophosphamide and busulfan with stem cell rescue in patients with newly diagnosed PCSNL. Primary endpoint will be 1-year event-free survival and acute treatment-related toxicity.

2.2- Secondary objectives:

1- to evaluate response rates with the combination of rituximab and MPV as induction chemotherapy
2- to determine overall survival and progression-free survival with this regimen
3- To evaluate the incidence of treatment related neurotoxicity with this regimen.

3.0 BACKGROUND AND RATIONALE

3.1- Treatment for PCNSL

PCNSL is a non-Hodgkin's lymphoma (NHL) that arises within the brain, eyes, leptomeninges or spinal cord, in the absence of systemic disease. Despite being a relatively rare tumor, its incidence has been increasing in the immunocompetent patient population over the past several decades.[1, 2]

Numerous reports have shown that the addition of pre-irradiation methotrexate (MTX) in doses of 1 g/m^2 or higher significantly improves patient survival. Currently, multiple treatment regimens using high dose MTX alone or in combination with other chemotherapeutic agents have been reported. Although response rates may reach 90% in some series, the incidence of relapses is high and progression free-survival ranges from 12 to 20 months. Relapse yields a reserved prognosis and is associated with decreased quality of life and survival. The median overall survival remains 30-60 months [3-6]. Moreover, patients successfully treated with chemoradiation are at risk for developing late delayed neurotoxicity[3, 7, 8]. The usual form of presentation of neurotoxicity is of a devastating subcortical dementia, with executive dysfunction, memory abnormalities, gait ataxia and incontinence. Neurotoxicity is associated with a fatal course in a majority of patients. The incidence of neurotoxicity increases with longer survival and it has been reported in up to 40% of patients treated with chemotherapy and radiation therapy. Elderly are at increased risk and the incidence in patients over 60 can be as high as 90%. Some studies reporting on the use of intensive chemotherapy regimens without RT in an attempt of decreasing the risk of neurotoxicity have demonstrated increased acute toxicity and/or less effective disease control.[5, 6, 9-11] Therefore, the optimal treatment for PCNSL remains controversial.

3.2- Methotrexate, procarbazine and vincristine for PCNSL

The rationale underlying the choice of drugs in PCNSL is based on two premises: demonstrated activity in non-Hodgkin's lymphoma and penetration of the blood-brain barrier (BBB). Successful regimens for non-Hodgkin's lymphoma such as CHOP have been unsuccessful in the treatment of PCNSL because of inability of these drugs to cross an intact blood-brain barrier. Although some areas of the tumor may have a disrupted BBB, several reports have demonstrated the presence of tumor cells beyond those areas, where the BBB is intact.[12]

Methotrexate is the single most important drug in PCNSL. Its activity has been demonstrated in several trials as a single agent [6] or in combination with other drugs[3-5, 9]. It has the ability of crossing an intact BBB when used in doses higher than 1g/m2. Procarbazine and vincristine are drugs that are active

in NHL and have a good penetration of the BBB. They have been incorporated in a variety of regimens for PCNSL, although the single contribution of these drugs is difficult to ascertain.[13]

The activity of the combination of methotrexate, procarbazine and vincristine was demonstrated in a prospective study conducted by the RTOG. That study enrolled 98 patients with newly-diagnosed PCNSL. The regimen consisted of IV MTX 2.5g/m2, IO MTX 12mg, vincristine 1.4g/m2 and procarbazine 100mg/m2, followed by WBRT. A complete response to chemotherapy was observed in 58% of patients and a partial response in 36%. Median progression-free survival was 24 months and overall survival was 36.9 months.[4] Another prospective study was conducted at Memorial Sloan-Kettering using a similar regimen, but with MTX in a dose of 3.5g/m2. The median overall survival was 60 months.[3] However, in both studies, the incidence of neurotoxicity by the time of reporting was high (15 and 25%, respectively). Nevertheless, MPV has been considered the standard of care by many institutions and in the proposed study, it will be used for achieving maximum response rates as induction chemotherapy.

3.3- The use of high-dose chemotherapy with autologous stem cell rescue in PCNSL

High-dose chemotherapy with or without radiotherapy with autologous stem transplantation has been proven to be an effective salvage treatment modality for refractory or relapsed NHL. In patients with chemosensitive disease, the long-term disease free survival may approach 40 to 50%. Some studies have suggested an improved outcome when high dose chemotherapy with bone marrow transplantation is used as part of the initial treatment of patients with poor prognosis/stage IV NHL.[14]

A study using high-dose chemotherapy and stem cell rescue for refractory or recurrent PCNSL was reported by Soussain et al. Induction chemotherapy with high-dose cytarabine and etoposide was given prior to stem cell harvesting to 22 patients. Two patients died after induction chemotherapy; eight patients achieved a CR; four a PR and one had SD; seven patients had refractory disease. High-dose chemotherapy consisted of thiotepa (250mg/mg), busulfan (10mg/kg) and cyclophosphamide (60mg/kg), followed by stem cell rescue and it was given to 20 patients. A CR was achieved in 16 patients, PR in two, SD in one; disease progressed in one patient. At least one death was direct consequence of treatment, from severe thrombocytopenia. Acute neurotoxicity developed in two patients (one of them is the one patient who died from bleeding). The other patient recovered. Chronic neurotoxicity developed in 5 patients, two of them died from it. Among those 5 patients, 3 had received prior RT, the other two were older than 60. That study demonstrated that the regimen utilized was feasible and effective, although cumulative toxicity inherent to patients with recurrent disease precluded better results.[9]

Encouraging results with high-dose chemotherapy and stem cell rescue in PCNSL were also reported by Cheng et al. Seven patients with unfavorable prognostic factors (KPS <50, age>60 or relapsed disease) were treated with an induction chemotherapy consisting of MTX 3.5g/m2, procarbazine 100mg/m2 and cytarabine 3 g/m2. A CR was obtained in one patient, a PR in 5 patients and PD in one. The high-dose regimen consisted of thiotepa 300mg/m2 and oral busulfan 4mg/kg, which achieved a CR in all patients. One early treatment-related death occurred in a patient with multiple comorbid medical conditions. Five patients were alive at 5, 8, 24, 36 and 42 months of follow-up. No neurotoxicity had been observed but no patient had been treated with RT. This study suggested that the use of drugs that cross the BBB for the high-dose chemotherapy part of the regimen may achieve better results than non-crossing agents.[15]

A study conducted in our institution treated 28 patients with newly-diagnosed PCNSL with MTX 3.5g/m2 and cytarabine (3g/m2) followed by BEAM chemotherapy and stem-cell rescue. Of the 25 patients evaluable for response, only 16 patients had a PR or better after MTX and proceeded to cytarabine. After cytarabine, 8 patients had a CR and 6 had a PR; those patients proceeded with HD

chemotherapy. The other two patients did not proceed with HD chemotherapy because of disease progression in one and systemic complications in another patient. Among the 14 patients who were treated with HD chemotherapy, a CR was achieved in 8 and PR in 2; disease progressed in three patients; one patient died from transplantation-related complications. The median event-free survival was 9.3 months. No neurotoxicity developed. The conclusions of this study were that a better induction regimen was necessary for improving response rates as to allow more patients to receive the high-dose chemotherapy and that BEAM may not be the optimal choice for high-dose chemotherapy because these drugs do not have a good CNS penetration.[10]Therefore, in the present study, MPV will be utilized for improving initial response rates; the regimen described by Soussain using thiotepa, busulfan and cyclophosphamide will replace BEAM in an attempt to decrease relapse rates, since these drugs have a better BBB penetration.

3.4- The role of Rituximab in PCNSL and NHL

Rituximab is a chimeric anti-CD20 monoclonal antibody designed to target the CD20 antigen which is a transmembrane phosphoprotein expressed on greater than 90% of all B-cell NHL's lymphoma. Data from patients with systemic lymphoma indicates that rituximab may increase the susceptibility of tumor cells to chemotherapy.

Ruhstaller et al evaluated the anti-tumor activity and CNS penetration of intravenously administered Rituximab in a 38-year old male with follicular lymphoma relapsing in the CNS. Rituximab 800 mg was administered intravenously once weekly for four weeks. Following therapy, marked neurologic improvement occurred and MRI showed reduction of leptomeningeal enhancement. Intrathecal cytarabine and hydrocortisone were then administered weekly alternating with intravenous Rituximab for two months and then alternating every two weeks for 3 months (total 12 Rituximab infusions and 5 intrathecal chemotherapies). Eight months after initiating this regimen, neurological evaluation was normal and repeat MRI showed near complete disappearance of CNS lesions. Rituximab peripheral blood and cerebral spinal fluid (CSF) levels were measured 4 days after the sixth infusion and immediately after the seventh infusion. The CSF concentration was 1.76% (10 uG/ml) and 1.04% (8.5 ML/ml) of the corresponding serum levels after the sixth and seventh infusions, respectively. Despite being a heavy molecular weight, rituximab may penetrate the BBB via leakage across areas of BBB breakdown and/or macromolecular vesicular transport of the antibody across an intact BBB.[16]

At MSKCC we have treated 9 PCNSL patients using rituximab including 3 patients with refractory CD20 positive PCNSL treated with systemic Rituximab as single agent therapy. The first patient was a 61-year-old man who received Rituximab 375mg/m^2 administered IV once weekly for four doses. The patient achieved a radiographic partial response with clinical improvement. The second subject was a 39-year old woman with a left periatrial lesion who had a radiographic partial response and clinical stabilization following Rituximab administered as a 500 mg/m^2 dose for four weeks. The third patient was a 71-year old man with leptomeningeal disease who had no radiographic response after receiving 500 mg/m^2 of antibody for four doses. The other 6 patients received doses ranging between 500mg/m^2 and 750mg/m2.[17]

Wong et al. reported their experience using the combination of rituximab (375mg/m2) and temozolomide for PCNSL in 7 patients. That regimen was well tolerated and 5 patients had an objective response.[18] At MSKCC, 15 patients with relapsed or refractory PCNSL with a combination of temozolomide and Rituxan (750 mg/m2). A CR was observed in 6 patients and a PR in 2. grade 3 anemia,

thrombocytopenia and leukopenia was seen in 4 patients.[19]

In an ongoing clinical trial at MSKCC using the combination of rituximab 500mg/m2 and MPV, 15 patients have completed therapy and were deemed evaluable for response. After 5 cycles of R-MPV, 13 patients responded, but only 5/14 had a CR. However, after 7 cycles, 14 of the 15 patients achieved a CR, suggesting that the combination of Rituxan and MPV is effective in PCNSL. In that study, patients presenting with a CR will be treated with reduced dose RT (2340 cGy), while the remaining patients will be treated with 4500 cGy. Hematologic toxicity was the main adverse event, with 1 grade 3 thrombocytopenia, one grade 3, one grade 4 and one grade 5 neutropenia among 18 patients assessable for toxicity. Among non-hematologic toxicity, grade 3 nausea and vomiting occurred in one patient; elevated ALT developed in a grade 3 in one and grade 4 in another patient.[20]

Based on these encouraging results, Rituxan will be added to MPV in an attempt to improve response rates to induction chemotherapy, selecting more patients for the high-dose chemotherapy part of the treatment and maybe improving disease-free survival.

3.5- Rationale for this study

This study is an effort to build on the results of two prior MSKCC studies: 98-86 and 01-146.

The strategy of treating newly diagnosed PCNSL patients with high-dose chemotherapy and stem cell rescue was pioneered at MSKCC with the protocol 98-86. That study clearly demonstrated that this strategy is feasible and likely cured a proportion of patients. However, the two major concerns in analyzing the results of 98-86 were that too few patients had an adequate response to induction regimen and a substantial proportion of patients recurred early after stem cell rescue.

To improve response rates to induction chemotherapy, we will use an identical regimen as used in 01-146, consisting of 5-7 cycles of R-MPV. This strategy gives the potential additive benefit of combining immunotherapy and chemotherapy and the proven benefit of enhanced CR rates with 2 additional cycles of chemotherapy in select patients. Furthermore, assays of CD-34 counts in patients on 01-146 suggest that we should be able to collect adequate number of stem cells during induction chemotherapy. This is critical since many of these patients require urgent treatment and could not reasonably delay definitive therapy for 1-2 weeks to allow stem cell collection.

To improve the efficacy of the high-dose chemotherapy regimen, the present protocol will incorporate different drugs in comparison to protocol 98-96. That study used BEAM chemotherapy, a well tolerated regimen that is particularly safe in the elderly (over 60) population, which constitutes half of the patients with PCNSL. However, in that study, nearly 50% of patients relapsed within a few months after high-dose chemotherapy. A possible explanation for this lack of efficacy is that the drugs in BEAM may not achieve ideal levels in the CNS due to incomplete penetration of the BBB. A study by Soussain et al using high-dose thiotepa and busulfan with stem-cell support in PCNSL resulted in lower relapse rates, with acceptable toxicity[9]. A small study by Cheng et al using that same combination for PCNSL in patients with poor prognosis (elderly, poor functional status or recurrent disease), demonstrated that the regimen was effective and well tolerated in that population.[15] Those studies suggest that thiotepa and busulfan may be more effective than BEAM in preventing relapse in PCNSL and, therefore, we will utilize the regimen described by Soussain for the high-dose chemotherapy portion of our study.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1- Design

In this single arm, multi-institution, phase II trial, patients with newly-diagnosed PCNSL will undergo base-line clinical and radiographic evaluation, including neuropsychologic evaluation and will be initially treated with induction chemotherapy, which will consist of R-MPV (one cycle=14 days). After 5 initial cycles of R-MPV, all patients will be evaluated for response with an MRI.

4.1.1- Patients with CR after the initial 5 cycles will proceed with the HD-chemotherapy portion of the study.

4.1.2- Patients with SD or PR after the initial 5 cycles will receive 2 additional cycles of R-MPV and will then be reassessed with an another MRI. After 7 cycles, those with a CR, PR, or continued PR as compared with the baseline (pretreatment) MRI, will proceed to HD chemotherapy. After 7 cycles, patients with SD will be taken off study.

4.1.3- Patients with PD at any time or with PD after 7 cycles of R-MPV cycles will be taken off study.

4.1.4- Patients will be off study at the time of death. All patients will be followed for survival every 6 months throughout their lifetime. Survival status may be obtained by phone call, clinical visit or medical records (e.g. physician notes/laboratory results of clinic or hospital visit.

The response documented in the MRI after the 5^{th} or 7^{th} cycles of R-MPV will be considered response rate to induction chemotherapy. Patients selected for the HD-chemotherapy portion of the study will receive thiotepa, busulfan and cyclophosphamide followed by stem cell reinfusion. Response rates to high-dose chemotherapy will be assessed 3 months after stem cell infusion. Patients will have neuropsychologic evaluation 6 months after high-dose chemotherapy and every 6 months thereafter. All patients will be followed for survival.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1- Rituximab:

Mechanism of action: rituximab is a genetically engineered chimeric (murine and human) monoclonal antibody directed against the CD20 antigen found on the surface of normal cells and in high copy number on malignant B lymphocytes. The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes and B-cell non-Hodgkin's lymphomas, and the Fc domain recruits immune effector functions to mediate B-cell lysis. Rituximab is supplied as 100mg and 500mg of sterile, preservative-free, single-use vials. DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS
Preparation: Use appropriate aseptic technique. Withdraw the necessary amount of Rituximab and dilute to a final concentration of 1 to 4 mg/ml into an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bat to mix the solution. Discard any unused portion left in the vial.

5.2- Methotrexate:

Mechanism of action: Inhibition of dihydrofolate reductase leads to partial depletion of reduced folates, which leads to inhibition of purine and thymidylate biosynthesis.

Formulation: Methotrexate sodium for injection is supplied as a sterile lyophilized powder, which comes in 20 mg, 50 mg and 1 g, vials.
Preparation: Immediately before use the contents of each vial should be reconstituted with preservative free medium (5% dextrose solution USP or sodium chloride injection USP). The 20 and 50 mg vials should be reconstituted to a concentration no greater than 25mg/ml; the 1 g vial should be reconstituted with 19.4 ml to a concentration of 50 mg/ml. The drug is then further diluted with D5W for intravenous administration.
Storage: Vials should be stored at room temperature and protected from light.

5.3-Vincristine:
Mechanism of action: The mechanism of action of vincristine has been related to the inhibition of microtubule formation in the mitotic spindle, resulting in an arrest of dividing cells at the metaphase stage.
Formulation: Preparation of vincristine is for IV use, available in 1mg, 2mg and 5mg vials.
Preparation: Do not add extra fluid to the vial prior to removal of the dose. Withdraw the solution of vincristine into an accurate dry syringe, measuring the dose carefully.

5.4- Procarbazine:
Mechanism of action: Procarbazine may act by inhibition of protein, RNA and DNA synthesis. Studies have suggested that procarbazine may inhibit transmethylation of methyl groups of methionine into t-RNA. The absence of functional t-RNA could cause the cessation of protein synthesis and consequently DNA and RNA synthesis.
Formulation: Procarbazine is available as capsules containing the equivalent of 50 mg procarbazine as the hydrochloride.
Preparation: Each capsule also contains cornstarch, mannitol and talc. Gelatin capsule shells contain parabens (methyl and propyl), potassium sorbate, titanium dioxide, FD&C yellow No. 6 and D&C Yellow No.10.
Storage: The drug is stored in room temperature.

5.5- Busulfan (Busulfex):
Mechanism of action: polyfunctional-alkylating agent that interacts with nucleic acids causing inter-strand cross-linking and DNA protein cross-linking. Busulfan is extensively metabolized to inactive compounds that are renally excreted.
Formulation: 60 mg vials for intravenous use
Preparation: Sterile solution in 10 ml single use clear glass ampoules each containing 60 mg of busulfan at concentration of 6 mg/ml for IV use
Storage: Refrigerated conditions between 2-8°C

5.6- Thiotepa (Thioplex):
Mechanism of action: cell cycle non-specific chemotherapeutic agent capable of killing cells in any phase of the cell cycle. Thiotepa forms covalent cross-links with DNA or DNA protein complexes, resulting in cytotoxic, mutagenic and carcinogenic effects.
Formulation: 15mg vials.
Preparation: vials containing 15mg of non-pyrogenic, sterile lyophilized powder

Storage: Refrigerated conditions between 2-8°C. Protect from light at all times.

5.7- Cyclophosphamide (Cytoxan):
Mechanism of action: alkylating agent that is metabolized to cytotoxic metabolites that form cross-links with DNA resulting in inhibition of DNA synthesis and function. It is active in all phases of the cell cycle.
Formulation: Available in 100, 200, 500 1,000 and 2,000 mg vials for intravenous use
Preparation: Standard IV fluid – D_5W; maximum concentration = 20 mg/ml; IVPB volume: for doses < 1500 mg, infuse in 25 ml D_5W; for doses > 1500 mg, infuse as straight drug.
Storage: Store vials at room temperature. Reconstituted vials are stable for 2 days at room temperature and 28 days under refrigeration. Refrigerated-infusions prepared in D_5W are stable for 24 hours. Room temperature-infusions prepared in D_5W are stable for 24 hours.

5.8- Filgrastim (G-CSF):
Mechanism of action: human protein involved in the promotion of the growth and maturation of neutrophil/granulocyte progenitors and the stimulation of functional activity.
Formulation: Prepared from recombinant DNA, G-CSF is supplied containing clear colorless sterile protein solution.
Storage: It can be stored at 2-6 C and is stable for at least 30 months.

5.9- Leucovorin: Mechanism of action: Leucovorin is an active chemical derivative of folic acid. It is useful as an antidote to drugs, which act as folic acid antagonists (methotrexate).

Formulation: 50 mg, 100 mg, and 350 mg vials to be reconstituted for intravenous use; 5mg and 25 mg tablets for oral use.

Preparation: Vials for intravenous use must be reconstituted with sterile diluent. If bacteriostatic water is used the product is stable for 7 days. If reconstituted with sterile water for injection it must be used immediately.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

6.1.1- All patients must have non-Hodgkin's lymphoma involving the brain, as demonstrated by CT or MRI and histologic confirmation by one of the following:

- i) A positive CSF cytology for lymphoma or a monoclonal lymphocyte population as defined by cell surface markers.
- ii) A biopsy of the vitreous or uvea demonstrating non-Hodgkin's lymphoma
- iii) Brain biopsy

6.1.2- Patients must be HIV-1 negative.

6.1.3- Patient must have left ventricular ejection fraction $\geq 50\%$

6.1.4- Patients must have no evidence of systemic lymphoma. This must be demonstrated by a CT scan of the chest, abdomen and pelvis prior to registration.

6.1.5- Patients must have adequate bone marrow function (defined as peripheral leucocyte count >3000 cells/mm3 and platelet count > 100,000 cells/mm3), liver function (bilirubin < 2.0 mg%), and adequate renal function (serum creatinine < 1.5 mg/dl or creatinine clearance > 50cc/min/1.73M2).

6.1.6- Men and women of reproductive potential must agree to use an acceptable method of birth control during treatment and for six months after completion of treatment.

6.1.7- Patients must be between 18 and 72 years-old.

6.1.8- Patients must sign an informed consent

6.3 Subject Exclusion Criteria

The following would exclude a patient from the study:

- Prior cranial irradiation
- Other active primary malignancy with the exception of basal cell carcinoma of the skin and cervical carcinoma in situ
- Pre-existing immunodeficiency such as renal transplant recipient
- Prior treatment with chemotherapy for CNS lymphoma.

7.0 RECRUITMENT PLAN

Patients will be recruited from the Neurology and Neurosurgery services. All patients will be seen by a Neuro-Oncology attending physician. Every effort will be made to include encourage eligible women and minorities to participate. All patients will be required to sign a written informed consent prior to being registered on this protocol. Every effort will be made to answer questions raised by patient and their family or advocate regarding the protocol and alternative therapies prior to asking a patient to sign the consent form.

Estimated accrual: based on previous clinical trials conducted at MSKCC, the estimated accrual is 3-4 patients/month. Estimated study duration: 2-3 years.

8.0 PRETREATMENT EVALUATION

8.1- Bloods: CBC with white cell differential, PT/PTT, screening profile including creatinine, electrolytes, and liver enzymes and EBV, CMV, HSV, hepatitis B and C serology.

8.2- HIV testing within 3 months prior to enrollment in the protocol. (Separate counseling and consent if done at MSKCC)

8.3- Urine: 24 creatinine clearance and routine urinalysis.

8.4- Radiographic studies: Chest X-ray (PA and lateral), CT scan of chest, abdomen and pelvis, MR scan of brain with gadolinium (CT scan may be substituted if patient has a medical contraindication to MR scanning) within 14 days of starting chemotherapy. MR spectroscopy will be done if available (not required for protocol).

8.5- Complete ophthalmologic exam including slit lamp.

8.6- A complete physical and neurological exam including KPS and MMSE.

8.7- Baseline neuropsychologic evaluation (appendix). If neuropsychological evaluation is not possible patients may still participate in the study.

8.8- Bone marrow biopsy and aspirate. Results of bone marrow biopsy and aspirate are not required for study enrollment, but if evidence of bone marrow lymphomatous infiltration is documented, then the patient should be taken off protocol since the patient no longer meets the definition of primary CNS lymphoma and therefore no longer meets eligibility criteria. Such patients will be treated at the discretion of treating physician and may continue with induction treatment off-protocol if deemed appropriate.

9.0 TREATMENT/INTERVENTION PLAN

9.1- Induction chemotherapy:

After registration and initial evaluation, patients will receive 5 cycles of the combination of Rituximab, methotrexate (MTX), procarbazine and vincristine (R-MPV). Rituximab will typically be administered on an outpatient basis. Patients will then be admitted to receive methotrexate, procarbazine, and vincristine as inpatients. One cycle was defined as 14 days and will consist of the following:

9.1.1- Rituximab 500 mg/m^2 will be given intravenously on day 1 of each cycle typically as an outpatient. Prior to Rituximab infusion, patients will be pre-medicated with lorazepam 0.5 mg - 1 mg IV, Benadryl 25-50mg IV/po, Tylenol 650 mg po. Demerol 25-50 mg will be given to the patient prn rigors. Rituximab will be infused over approximately 5 hours or per institutional guidelines.

9.1.2- Methotrexate, 3.5 gm/m^2, diluted in 500cc D5W containing 50meq NaHCO3 will be infused intravenously over approximately 2 hours on day 2 of each cycle. Standard pretreatment hydration and alkalinization of urine will be done per institutional guidelines (MSKCC: Infuse 1 liter D_5W + 100mEq sodium bicarbonate over 4 hours and urine output should be > 150 ml/hour and urine pH > 7.5 prior to the start of the high-dose Methotrexate). Prior to MTX administration, 1meq/kg of $NaHCO_3$ in 50cc D5W will be given. Oral $NaHCO_3$ (2 tabs po q 6h) will be given for the 3 days following MTX infusion to maintain urine pH > 7.0. If a patient is unable to take $NaHCO_3$ by mouth, or if adequate alkalinization of the urine is not accomplished, IV $NaHCO_3$ will be started. 15 meq NaHCO3 in 50 cc D5W are administered IV over 15 minutes q 6h; the frequency can be increased to every 4 hr if the urine pH remains < 7.0.
Leucovorin, 25 mg po q 6h for 12 doses, (if a patient is unable to take oral leucovorin, it will be administered IV at 20 mg q 6 hr) will begin approximately 24 hours after MTX infusion and continue for 72 hours or until the MTX level is < 1 X 10^{-8}.
MTX levels, CBC and electrolytes (including BUN/Cr) will be obtained daily for 3 days following MTX administration. If MTX levels are toxic at 48 hrs (>1 x 10^{-6} M), leucovorin will be increased to 40 mg po/IV q 4h and total fluid intake will increase to 3000 cc/m^2. MTX levels > 1 X 10^{-8} at 72 hr will dictate continued leucovorin (40 mg po/IV q 6h), hydration at 3000 cc/m^2/day and $NaHCO_3$ (or per institutional guidelines) until MTX level is 1 X 10^{-8} or less.

All patients will be instructed to maintain vigorous oral hydration throughout the MTX infusion and for 72 hours thereafter. For the first 24 hours after the MTX administration, total fluid intake should be at least 1500-1800 cc/m^2 and increased to 2000 cc/m^2 for the following 48 hours. Patients will be instructed to refrain from eating citrus fruit, drinking citrus fruit juices or taking vitamin C supplements during MTX administration and for the following 72 hrs.

9.1.3- Vincristine 1.4mg/m^2 IV will be given concomitantly with each dose of systemic MTX. Vincristine is capped at 2mg/m^2 (or 2.8mg maximum dose).

9.1.4- Procarbazine, beginning on day 2, 100mg/m^2/day PO for 7 days will be given with the first, third, fifth, and seventh (if patient receives this) cycle of R-MPV. Patients will be maintained on a tyramine-free diet during procarbazine administration.

9.1.5- G-CSF support should be used with each cycle of induction chemotherapy. Patients will be treated with 5ug/kg/day subcutaneously daily for 3-5 days starting 24 hours after their last dose of procarbazine (cycles 1,3,5,7) or starting 96 hours after MTX dose or when MTX level is $< 1 \times 10^{-8}$ (cycles 2,4,6). If for any reason a patient cannot receive GCSF then a CBC should be done at least twice a week between cycles of induction chemotherapy and between cycle 7 and the start of high-dose chemotherapy.

9.1.6- All patients will undergo a repeat brain MRI (or CT) after 5 cycles. The response achieved will determine the total number of cycles as follows:

-CR: Patients with CR after the initial 5 cycles will proceed with the HD- chemotherapy portion of the study.

-SD or PR: Patients with SD or PR after the initial 5 cycles will receive 2 additional cycles of R-MPV and will be reassessed with an MRI. After 7 cycles, those with a CR, PR, or continued PR as compared with the baseline (pretreatment) MRI, will proceed to HD chemotherapy. After 7 cycles, patients with SD will be taken off study.

-PD: Patients with PD after 5 cycles of R-MPV or after 7 cycles of R-MPV or with PD at any time during the study will taken off study.

9.2- Peripheral Blood Stem Cell Cytapheresis

The peripheral blood stem cell (PBSC) harvest procedure will be performed at the discretion of the hematology attending (usually after the 1st or 2nd cycle of R-MPV). Cytapheresis will start after bone marrow recovery and repeated daily up to day 7 until a target yield of $> 5 \times 10^6$ CD34+ cells have been collected; the minimum acceptable total yield is 2×10^6 CD 34+ cells/kg. If fewer than 2×10^6 CD34+ cells are collected then bone marrow harvest is required. The minimum acceptable yield for patients undergoing bone marrow harvest is 1.5×10^8 mononuclear cells/kg.

Some patients will have inadequate peripheral venous access and require placement of a catheter suitable for hemodialysis. All patients will have a 13.5 Fr Davol double-lumen catheter (or similar catheter) placed prior to PBSC leukophoresis. If this catheter requires replacement subsequently, a standard 10 Fr catheter may be used.

9.3- HD chemotherapy with autologous stem cell support

9.3.1- The high-dose chemotherapy program will include thiotepa, busulfan and cyclophosphamide administered as follows:

Agent	Total Dose	Route	Days
Thiotepa	250 mg/m2/day	intravenous	-9, -8, -7
Busulfan	3.2 mg/kg/day	intravenous	-6, -5, -4
Cyclophosphamide	60mg/kg/day	intravenous	-3, -2

9.3.2- Stem cell reinfusion occurs on day 0 and will follow institutional standard procedures. (Please see appendix for general recommendations)

[NOTE: When patient weight exceeds the maximum *large frame* value from the Metropolitan Life table, doses of chemotherapy will be based on ideal body weight, not actual weight (ie. the maximum large frame weight from said table).]

9.3.2- Support therapy
Support therapy during high-dose chemotherapy and post-transplant care will follow institutional guidelines and usually will include the following:

- Seizure prophylaxis: all patients should be on prophylactic anticonvulsants prior to the administration of busulfan. The general recommendation in patients not already on an anticonvulsant is to use a benzodiazepine (clonazepam 2mg/day or diazepam 10mg/day) starting the first day of busulfan administration and continuing until the day after the last dose of busulfan.

- Hydration: To ensure a urine output >100 ml/hr patients will receive normal saline at 200 $ml/m^2/hr$ x 6 hours prior to commencing high-dose chemotherapy. Normal saline plus 20 (milliequivalents) of KCL/l will be infused intravenously between doses of busulfan and thiotepa and during the rest phase prior to stem cell reinfusion. Subsequently, intravenous fluid requirements will be dictated by oral intake and other factors. Fluid intake and output will be continuously measured. If there is a lag in urine output greater than 800 ml/12 hours, furosemide or an equivalent diuretic should be administered intravenously (± low dose dopamine). Prior to cyclophosphamide infusion hydration will consist of $D_5$1/2 NS + 8 mEq magnesium sulfate/Liter + 20 mEq potassium chloride/liter and $D_5$1/2 NS + 20mEq potassium chloride/Liter + 50 mEq sodium bicarbonate/Liter to infuse simultaneously or alternate bottle sequence (prefer simultaneous infusion). Start IV hydration with each liter at 75 ml/hour to total 150 ml/hour at 7 PM the night before, then increase IV rate to 300 ml/hour (each liter at 150 ml/hour) at 7AM the next day. After the infusion, hydration will consist of $D_5$1/2 NS + 8 mEq magnesium sulfate/Liter + 20 mEq potassium chloride/Liter

and $D_5$1/2 NS + 20 mEq potassium chloride/Liter + 50 mEq sodium bicarbonate/Liter to infuse simultaneously or alternate bottle sequence (prefer simultaneous infusion) @ 300 ml/hour (each liter at 150 ml/hour) for 24 hours after last dose of cyclophosphamide. Lasix will be given as needed. Urinalysis will be sent stat every 4 hours for 24 hours post treatment and monitored for hematuria.

- Anti-emesis: All antiemetic prophylaxis will be done according to standard institutional procedures. (Please see appendix for general recommendations).

- Patients will be given vitamin K 10 mg po or sq one to three times per week unless added to TPN.

- Patients will start G-CSF 5 ug/kg sq bid beginning day +1. It will be continued until ANC > 1000/mm3 X 3 days.

- Blood transfusion: All blood products will be irradiated to 3000 cGy to prevent transfusion associated GVHD. Platelets will be given prophylactically to maintain a platelet count > 20,000/mm3 for the first 10 days post PBPCT in all patients and beyond that period in patients with active bleeding, fever or coagulopathy. After day 10 prophylactic platelet transfusions will be given to maintain a platelet count > 10,000/mm3 in the low risk, non-bleeding patient. Patients will be transfused to maintain a hemoglobin > 7 g/dl. If clinically indicated, additional transfusions can be given. Patients who are CMV seronegative will receive white blood cell depleted products using a third generation white cell filter, or CMV negative blood products.

- Nutritional status will be carefully monitored by the physician and the dietician. TPN will be administered to patients if caloric intake is < 25% of his/her estimated calorie needs for 3 days.

- Antibiotics: On admission, patients will receive:

  - Ciprofloxacin 500 mg po bid which will be continued until the patient requires broad spectrum antibiotics for neutropenic fever.

  - Fluconazole 100 mg po or IV bid which will continue until the ANC is > 1000/mm3 X 3 days or until amphotericin B therapy is initiated (except for patients concurrently enrolled on MSKCC protocol 97-112, who will not receive fluconazole prophylaxis).

  - Bactrim ds po bid until day -2 for PCP prophylaxis.

  - Nystatin powder will be applied to the groin and axilla bid.

  - Patients seropositive for HSV will be given acyclovir 400 mg po bid or 250 mg IVPB q 8h until the ANC > 1000/mm3 X 3 days. Acyclovir will be restarted upon discharge at 400 mg po bid for 90 days post PBPCT.

- On day 60 post PBPCT patients will receive aerosolized pentamidine. On day 90 if the platelet count is > 50,000/ul Bactrim will be restarted at 1 po bid for 2 consecutive days/weeks for 180 days post PBPCT. If on day 90 the platelet count is < 50,000/ul aerosolized pentamidine will continue monthly until day 180 post PBPCT.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1- During induction chemotherapy:

Electrolytes including BUN/Cr and MTX level will be drawn daily prior to and for at least 72 hours after each cycle of MTX. (1 st MTX level 24 hr after infusion).
Urine pH will be checked several times daily for at least 72 hours after each cycle of MTX until MTX levels are not toxic. CBC will be checked twice weekly until WBC and platelets have recovered.

Evaluation of response will take place after 5 or 7 cycles of R-MPV and 90 days after chemotherapy. At each step, the following tests will be performed:

-Complete neurologic examination including KPS and MMSE.

-MRI of the brain with gadolinium to evaluate response to treatment. MR spectroscopy will be done if available (not required). CT scan will be performed in case of contra-indications to MRI.

-If CSF cytology was positive at initial diagnosis, repeat CSF will be sent for cytologic examination, and routine chemistries and cell count.

-Patients with ocular involvement at diagnosis will have a complete eye exam including slit lamp examination.

10.2 Evaluation prior to HD-chemotherapy/PBPCT :

- Pulmonary function tests, including DLCO

- Dental evaluation prior to hospitalization for PBPCT.

- Echocardiogram or MUGA scan.

- CBC, electrolytes, liver function.

- Neuropsychological evaluation will be performed upon completion of R-MPV (induction chemotherapy) and prior to transplant.

10.3 Post treatment evaluation:

Patients will be examined at least weekly until they become transfusion independent.
Follow-up neurologic status will be assessed monthly for the first 3 months post PBPCT and approximately every 3 months thereafter for the first two years. Follow up will then be done every 4 months for third year and fourth years and then every 6 months throughout their lifetime. Survival status may be obtained by phone call, clinical visit or medical records (e.g. physician notes/laboratory results of clinic or hospital visit).

. All neurologic evaluations will include a MMSE and KPS. An MRI scan will be done at the time of each neurologic evaluation beginning at 3 months post PBPCT.

Repeat CSF and/or ocular exam will be done 3 months post PBPCT in those patients who had evidence of involvement at diagnosis. Further exams will only be done for recurrent symptoms.

Neuropsychologic evaluation will be repeated approximately 6 months after the completion of therapy and at 6 months intervals thereafter.

11.0 TOXICITIES/SIDE EFFECTS

Toxicity will be graded using the NCI Common Toxicity Criteria, version 3.0.

11.1- Rituximab may cause infusion-related symptoms, consisting of fever and chills that occurs in most patients during the first infusion. Other hypersensitivity symptoms, including nausea, urticaria, fatigue, headache, pruritus, bronchospasm, dyspnea, sensation of tongue or throat swelling, rhinitis, vomiting, hypotension, flushing, and pain at disease sites, may also be seen. They occurred primarily during Rituximab infusion and resumption at a slower rate.
Other adverse events caused by Rituximab include neutropenia, thrombocytopenia and asthenia. Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during Rituximab infusions.
Although rare, tumor lysis syndrome has been reported in post-marketing studies and is characterized in patients with a high number of circulating malignant cells (>25,000 ul) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia.
In rare cases, severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have occurred (4-7/10,000 patients or 0.04-0.07%) Nearly all fatal infusion-related events occurred in association with the first infusion.
The following immune serious adverse events have been reported to occur rarely (<0.1%) in patients following completion of Rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), eye disorders (uveitis and optic neuritis), and severe bullous skin reactions (including toxic epidermal necrolysis and pemphigus) that may result in fatal outcomes. Patients may have these symptoms alone or in combination with rash and polyarthritis.

11.2- MTX can produce myelosuppression, GI toxicity, particularly mucositis, liver dysfunction, renal

failure and rarely interstitial pneumonitis and gastrointestinal epithelial denudation.

11.3- Procarbazine can produce myelosuppression, nausea and vomiting. Hypertension can occur when foods containing tyramine are ingested due to inhibition of monoamine oxidase, and Antabuse-like reactions may occur when alcohol is taken with PCB. Cutaneous and pulmonary hypersensitivity reactions are rare complications.

11.4- Vincristine can cause a peripheral neuropathy including autonomic dysfunction such as constipation. It also causes alopecia and can result in local necrosis after extravasation.

11.5- Busulfan can cause moderate nausea and vomiting, diarrhea, dose limiting mucositis, and severe myelosuppression with high dose therapy. Severe or irreversible effects include veno-occlusive disease (VOD) of the liver, seizures, confusion, hyperpigmentation of the skin, interstitial pulmonary fibrosis ("busulfan lung"), increased incidence of secondary malignancies after prolonged administration. Because of the risk of seizures, prophylactic anti-convulsants are recommended.

11.5- Thiotepa can cause bone marrow depression, which is dose limiting and requires stem cell support at doses >60 mg/m^2. Neutropenia and thrombocytopenia occur within 7 to 10 days. Other common side effects include nausea and vomiting (usually mild), mucositis, esophagitis and enterocolitis. Dermatological toxicity consisting of an acute erythrodermia with desquamation and peeling of skin of soles and palms is uniformly seen. General darkening of the skin may occur (resembling a mild suntan) which can persist for several months. Central nervous system toxicity characterized by inappropriate behavior, forgetfulness, confusion and somnolence occurs in ~5% patients given 900 mg/m^2.

11.6- Cyclophosphamide can cause dose dependent myelosuppression. Bladder toxicity in the form of hemorrhagic cystitis, dysuria, and increased urinary frequency occurs in 5-10% of patients. It is usually reversible upon discontinuation of the drug. Uroprotection with mesna and hydration must be used with high-dose therapy. Nausea and vomiting usually occur within 2-4 hours after infusion. Alopecia is severe and skin and nails may become hyperpigmented. Amenorrhea with ovarian failure may occur and sterility may be permanent. Cardiac toxicity may be observed. Secondary malignancies may develop, including acute leukemia and bladder cancer. Immunosuppression, SIADH and hypersensitivity reactions may occur.

11.6- Filgrastin can cause bone pain, exacerbation of pre-existing autoimmune disorders, transient and reversible changes in alkaline phosphatase, uric acid and LDH.

11.7- Leucovorin can cause allergic reactions.

12.0 CRITERIA FOR THE THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Radiographic response:
As assessed by MRI/CT. Tumor measurements must be recorded in centimeters and must be measured at the longest diameter and its perpendicular at the widest portion of the tumor. For tumors that are difficult to measure (ie. irregular shape), a visual interpretation of the magnitude of response is acceptable.

• Complete response (CR) - disappearance of all enhancing tumor. Patients must be off steroid therapy and neurologically stable or improved. If CSF cytology was previously positive, it must be reassessed and negative. If ophthalmologic examination was previously positive, it must be reassessed and negative for cells.

• Partial response (PR) - > 50 % decrease in tumor size in comparison with baseline scan. Patients must be neurologically improved or stable on a stable or decreasing dose of corticosteroids.
• Progressive disease (PD) - > 25% increase in enhancing tumor or the appearance of new lesions. The patient may be neurologically stable or worse and on stable or increasing doses of steroids.
• Stable disease (SD) - all other situations.

13.1 CRITERIA FOR REMOVAL FROM STUDY

Patients may be removed from the study if any one or more of the events listed below occurs. The reason for removal and the date are to be recorded. An end of study treatment evaluation should be performed whenever possible.

- Ineligibility of the patient as defined in the inclusion/exclusion criteria
- Significant protocol violation
- Non-compliance of the patient
- Unacceptable toxicity
- Refusal of the patient to continue treatment and/or observations
- Unrelated medical illness or complication
- Disease progression or a requirement for an alternative therapy
- Decision by the investigator that termination is in the patient's best medical interest or as an administrative decision
- Loss to follow-up
- Death of the patient.

14.0 BIOSTATISTICS

14.1- The primary end-point will be one-year event-free survival, defined as time from diagnosis to tumor relapse, progression or death. An exact binomial test with a nominal 0.050 one-sided significance level will have 90% power to detect the difference between the null hypothesis proportion, π_0 of 0.5 (estimated 1-year event-free survival with chemotherapy only regimens) and the alternative proportion π_A, of 0.750 when the sample size is 33 patients.

14.2- Early stopping rule: If more than two toxic deaths occur among the first 15 patients, the study will be stopped. The study will also be stopped if four toxic deaths occur at anytime. If the true risk of toxic death is 16% or higher, then the probability of seeing 4 toxic deaths (and stopping the trial) will be at least 80%.

14.3- Secondary end-point will include response rate to induction chemotherapy, response rate to high-dose chemotherapy, progression-free and overall survival, and incidence of neurotoxicity. Survival curves will be constructed using Kaplan-Meier method. Overall and induction response rates will be reported with a confidence interval. With a total of 33 patients, response rates will be estimated with a 95% confidence interval to +/- 13%.

14.4- All patients will be included in the analysis in an intent-to-treat fashion.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

All patients will be registered into the Clinical Research Database at Memorial Sloan Kettering Cancer Center. Registration should be complete prior to initiation of therapy. There is no planned randomization.

15.2 RESEARCH PARTICIPANT REGISTRATION

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.
Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.
During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.
All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

15.3 Randomization

N/A

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

Data will be collected centrally at Memorial Sloan Kettering Cancer Center. For each patient, the following forms will be completed and submitted:

Form	To be completed
Eligibility I/On-Study	Prior to registration
Consent	Prior to registration
Induction Chemotherapy	At time of registration on study

Central Pathology Review	Prior to registration
Eligibility II	Prior to busulfan + thiotepa + cyclophosphamide
H-D Chemotherapy	After busulfan + thiotepa + cyclophosphamide
Follow-up	q3monthly x 2 yrs, then q6monthly x 3 yrs, then yearly
Final Report	At progression or death
Adverse Events	Within 10 days

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

17.1 PROTECTION OF HUMAN SUBJECTS

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2- Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- *List any additional events that require SAE reporting (pregnancy, AEs of special interest (AESI), secondary malignancies, etc)*

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.
The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

17.3- Risks to human subjects
Potential risks to human subjects include drug related toxicity, pain and discomfort associated with phlebotomy, and possible psychologic discomfort while obtaining MRI scans.
The side effects and potential toxicities of all chemotherapeutic agents are listed in section 11. Death may occur as a result of treatment. All efforts will be made to avoid any complication by completely reviewing patients' symptoms and monitoring blood tests.

Periodic phlebotomy is necessary to monitor for the potential treatment related toxicities; trained phlebotomy technicians or nurses will perform all phlebotomy.

MRI scans are the accepted and best method for assessing central nervous system tumors and patients with substantial anxiety can be treated with an anxiolytic prior to the study. In those patients where an MRI is not possible for medical reasons (eg. pacemaker, ferromagnetic intracranial aneurysm clips) a CT scan will be obtained instead.

17.4- Potential benefit to society will be the establishment of an effective medical therapy, which may offer prolonged survival or improved quality of survival to other patients with this disease. Potential benefit to society will be the enhanced productivity and decreased cost of any individual spared progressive neurologic impairment.

17.5- If an adverse medical event occurs, the patient will first contact the principal investigator or treating physician. At nights and on weekends, there is a neuro-oncology physician on call at all times. Patients may either call or come directly to the urgent care center at Memorial Hospital (or their collaborating institution) to be seen.

17.6- Costs to the patient will include the cost of the chemotherapy, MRI scans, office visits, blood tests and any hospital admission including those admissions as a consequence of treatment-related complications.

17.7- All serious adverse events incurred while a patient is on study will be reported to the IRB at Memorial Hospital. All serious adverse experiences and relevant laboratory findings must be reported to Dr. Christian Grommes immediately. An adverse experience is considered serious if death occurs, the condition is life threatening, hospitalization is required, prolonged hospitalization results, or there is permanent disability or incapacity. All information regarding serious adverse experiences must be recorded on the form provided. Patients suffering serious adverse reactions must be carefully followed and all follow-up information also recorded. In addition, all life threatening and lethal (grade 4 or grade 5) known, unknown, or suspected reactions (toxicities) must be reported to Dr. Christian Grommes by telephone (212) 639-4058, or fax (212) 718-3296. A written report must be sent within ten days to Dr. Christian Grommes, Department of Neurology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10021. Any death, regardless of cause, must be reported to Dr. Christian Grommes by telephone or fax and in writing. It is the treating physician's responsibility to investigate and report the date and cause of death of any patient entered on this trial. All unusual reactions (grade 2 or 3 toxicities) must be reported in writing within 10 days to Dr. Christian Grommes. To protect patient confidentiality, names or other identifying characteristics will not be used in any reports or publications resulting from this study. Patient records relating to this study will be stored in the department of Neurology; access to these records will be restricted to study investigators, appropriate institutional and federal review agencies. Samples of peripheral blood, bone marrow, CSF or tumor will be anonymized before storage.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from

the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.
Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES