Appendix (online only)

Rituximab, Methotrexate, Procarbazine and Vincristine Followed by High-Dose Chemotherapy with Thiotepa, Busulfan and Cyclophosphamide and Autologous Stem-Cell Transplant for Newly Diagnosed Primary CNS Lymphoma

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2) Results of Neuropsychological Testing

3) Protocol details on eligibility, treatment and study assessments
DLBCL: Diffuse large B-cell lymphoma; R-MPV: Rituximab, methotrexate, procarbazine, vincristine; CR: Complete response; CRu: unconfirmed complete response; PR: Partial response; SD: Sable disease; PD: Progression of disease; TBC-ASCT: Thiotepa, busulfan and cyclophosphamide followed by autologous stem-cell transplant
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SD- Standard Deviation; TMTA-Trail Making Test Part A; TMTB-Trail Making Test Part B; BTA-Brief Test of Attention; COWAT- Controlled Word Association Test; HVLT-R-TL-Hopkins Verbal Learning Test-Revised- Total Learning; HVLT-R-DEL-Hopkins Verbal Learning Test-Revised - Delayed Recall; HVLT-R-DI-Hopkins Verbal Learning Test-Revised-Discrimination Index; GPTD-Grooved Pegboard Test-Dominant Hand; GPTND-Grooved Pegboard Test-Non-Dominant Hand; BDI-Beck Depression Inventory; FACT-
BR-Functional Assessment of Cancer Therapy-Brain Cancer; % imp.-percentage of patients with impaired scores. Z-scores ≤ 1.5 represent impairment.

1 GPT-D/ND at baseline n=10; at all follow-up assessments, n=13.

In order to capture the long-term cognitive effects in survivors, this analysis focused on patients who were disease-free at the 24-month post-transplant time point and that agreed to complete neuropsychological evaluations up to that point (N=16).
CRITERIA FOR SUBJECT ELIGIBILITY

Subject Inclusion Criteria
1- All patients must have non-Hodgkin's lymphoma involving the brain, as demonstrated by 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
2- Patients must be HIV-1 negative.
3- Patient must have left ventricular ejection fraction ≥ 50%
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.
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- 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.
7- Patients must be between 18 and 72 years-old.
8- Patients must sign an informed consent

Subject Exclusion Criteria
The following would exclude a patient from the study:
1- Prior cranial irradiation
2- Other active primary malignancy with the exception of basal cell carcinoma of the skin and cervical carcinoma in situ
3- Pre-existing immunodeficiency such as renal transplant recipient
4- Prior treatment with chemotherapy for CNS lymphoma.

PRETREATMENT EVALUATION
- Blood: CBC with white cell differential, PT/PTT, screening profile including creatinine, electrolytes, and liver enzymes and EBV, CMV, HSV, hepatitis B and C serology.
- HIV testing within 3 months prior to enrollment in the protocol. (Separate counseling and consent if done at MSKCC)
- Urine: 24 creatinine clearance and routine urinalysis.
- Radiographic studies: Chest X-ray (PA and lateral), CT scan of chest, abdomen and pelvis, MR scan of brain with gadolinium within 14 days of starting chemotherapy. MR spectroscopy will be done if available (not required for protocol).
- Complete ophthalmologic exam including slit lamp.
- A complete physical and neurological exam including KPS and MMSE.
- Baseline neuropsychologic evaluation. If neuropsychological evaluation is not possible patients may still participate in the study.
- 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.
- Lumbar puncture (if not contraindicated by mass effect) for CSF analysis, including CSF cytology.

PROTOCOL TREATMENT INSTRUCTIONS

In this trial, patients were treated as per the instructions below, which reflect MSKCC guidelines at the time the study was conducted. Please note that MSKCC guidelines are constantly evolving and current practice may have changed since.

**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:

- **Rituximab 500 mg/m²** 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.

- **Methotrexate, 3.5 gm/m²**, 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 D5W + 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 NaHCO3 in 50cc D5W will be given. Oral NaHCO3 (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 NaHCO3 by mouth, or if adequate alkalinization of the urine is not accomplished, IV NaHCO3 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/m². MTX levels > 1 X 10⁻⁸ at 72 hr will dictate continued leucovorin (40 mg po/IV q 6h), hydration at 3000 cc/m²/day and NaHCO₃ (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/m² and increased to 2000 cc/m² 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.

- Vincristine 1.4mg/m² IV will be given concomitantly with each dose of systemic MTX. Vincristine is capped at 2mg/m² (or 2.8mg maximum dose).

- Procarbazine, beginning on day 2, 100mg/m²/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.

- 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 X 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.

- 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 be taken off study.

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 $2 \times 10^6$ CD 34+ cells/kg. If fewer than $2 \times 10^6$ CD34+ cells are collected then bone marrow harvest is required. The minimum acceptable yield for patients undergoing bone marrow harvest is $1.5 \times 10^8$ 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 leukapheresis. If this catheter requires replacement subsequently, a standard 10 Fr catheter may be used.

HD chemotherapy with autologous stem cell support

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

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<th>Total Dose</th>
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<td>Cyclophosphamide</td>
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- Stem cell reinfusion occurs on day 0 and will follow institutional standard procedures.

[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).]

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/m²/hr × 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 D₅1/2 NS + 8 mEq magnesium sulfate/Liter + 20 mEq potassium chloride/liter and D₅1/2 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 D₅1/2 NS + 8 mEq magnesium sulfate/Liter + 20 mEq potassium chloride/Liter and D₅1/2 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.

- **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 PBPC 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.

**Evaluation during treatment/intervention**

**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. (1st 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.

**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.

**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 the second and third years and then every 6 months until the 5th year. 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.
THERAPEUTIC/DIAGNOSTIC AGENTS

- **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 bag to mix the solution. Discard any unused portion left in the vial.

- **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.

- **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.
**- 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.

**- 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

**- 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.

**- 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$_5$W; maximum concentration = 20 mg/ml; IVPB volume: for doses < 1500 mg, infuse in 25 ml D$_5$W; 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$_5$W are stable for 24 hours. Room temperature-infusions prepared in D$_5$W are stable for 24 hours.
- **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.

- **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.