A PHASE II CLINICAL TRIAL OF INDUCTION CHEMOTHERAPY WITH GEMCITABINE, PACLITAXEL AND OXALIPLATIN (GemPOx) FOLLOWED BY A SINGLE CYCLE OF MARROW-ABLATIVE CHEMOTHERAPY AND AUTOLOGOUS HEMATOPOIETIC PROGENITOR CELL RESCUE (AuHPCR) FOR PATIENTS WITH RECURRENT OR PROGRESSIVE CENTRAL NERVOUS SYSTEM GERM CELL TUMORS

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List of Abbreviations

AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate transaminase
AUC	Area Under the Curve
AuHPCR	Autologous Hematopoietic Progenitor Cell Rescue
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CNS	Central Nervous System
CNS GCT	Central Nervous System Germ Cell Tumors
CR	Complete Response
CRU	Complete Response with Unconfirmed Residual
CSA	Canadian Standards Association
DI	Diabetes Insipidus
DSMO	dimethyl sulfoxide
EFS	Event-free Survival
FDA	Food and Drug Administration
G-CSF	Granulocyte-Colony Stimulating Factor
GTS	Growing Teratoma Syndrome
HCGβ	Beta Human Chorionic Gonadotropin
HDC	High Dose Chemotherapy
Hgb	Hemoglobin
HPC	Hematopoietic progenitor cells

ICP	Intracranial Pressure
IRB	Institutional Review Board
MiRNA	microRNA
MMGCT	Mixed Malignant Germ Cell Tumors
NCH	Nationwide Children's Hospital
OS	Overall Survival
PD	Progressive Disease
Plts	Platelets
PR	Partial Response
PRBC	Packed Red Blood Cell
RBC	Red Blood Cell
RT	Radiation Therapy
SD	Stable Disease
SR	Sufficient Response
TMP/SMZ	Trimethoprim/sulfamethoxazole
TPN	Total Parental Nutrition
TTF	Time to Treatment Failure
ULN	Upper Limit Normal
VGPR	Very Good Partial Response
VP-16	Etoposide

1.0 ABSTRACT

Patients with pure germinoma of the central nervous system (CNS) have a high rate of cure, while only about two-thirds of patients with CNS non-germinomatous or mixed malignant germ cell tumors (MMGCT) are cured following upfront therapy. Even after recurrence, patients with intracranial germinoma have a higher likelihood of achieving remission with the known active chemotherapy agents. On the other hand, when relapses occur in patients with intracranial MMGCT, it is difficult to cure these patients with commonly used salvage chemotherapy regimens and therefore these patients have poor outcomes. To date, the best results have been achieved by employing a two-stage approach: initial intensive chemotherapy to achieve minimal residual tumor, followed by high-dose chemotherapy (HDC) with autologous hematopoietic progenitor cell rescue (AuHPCR). This approach has been reported in two multi-center studies to produce no more than 50% cure rates for patients with recurrent CNS germ cell tumors (GCT). A critical component of success here is the ability to achieve a state of minimal residual tumor with induction chemotherapy, prior to consolidation with HDC. Identifying new drugs and drug combinations to maximize achievement of minimal residual, especially in patients with MMGCT is required. A body of preclinical and clinical data in recurrent systemic germ cell tumors in adults has provided a strong rationale for evaluating the combination of gemcitabine, paclitaxel and oxaliplatin (GemPOx) in a multi-institutional phase II clinical trial for progressive or recurrent CNS GCT.

This study includes an induction phase consisting of the GemPOx chemotherapy combination. Following induction, only patients with MMGCT who have achieved a sufficient response to the GemPOx regimen will undergo consolidation with a single HDC cycle followed by AuHPCR. The decision to administer irradiation following study therapy will be left to the individual investigators. Patients with intracranial germinoma who have achieved a sufficient response will receive further treatment at the discretion of the treating physician. The primary aim of this phase II trial is to determine the response rates and the toxicities to the GemPOx combination, and the secondary aim is to optimize survival in patients with CNS GCTs, especially in those with MMGCT.

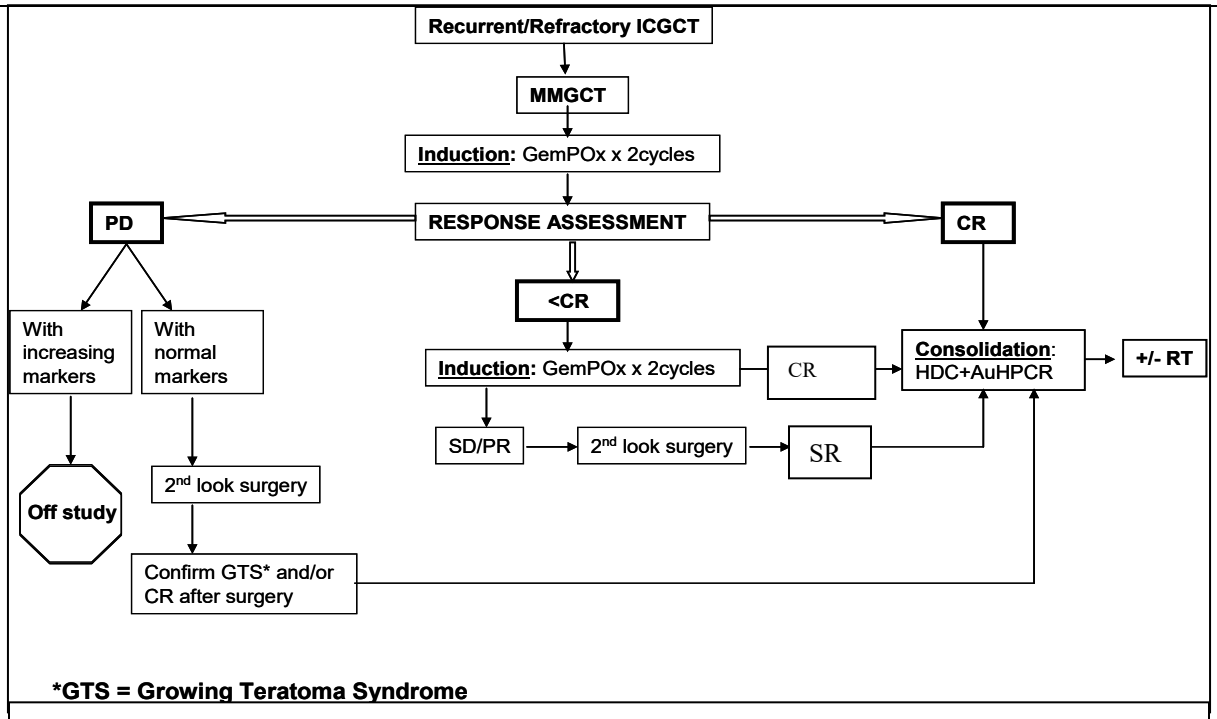


Figure 1: EXPERIMENTAL SCHEMA FOR MIXED MAILIGNANT GERM CELL TUMOR

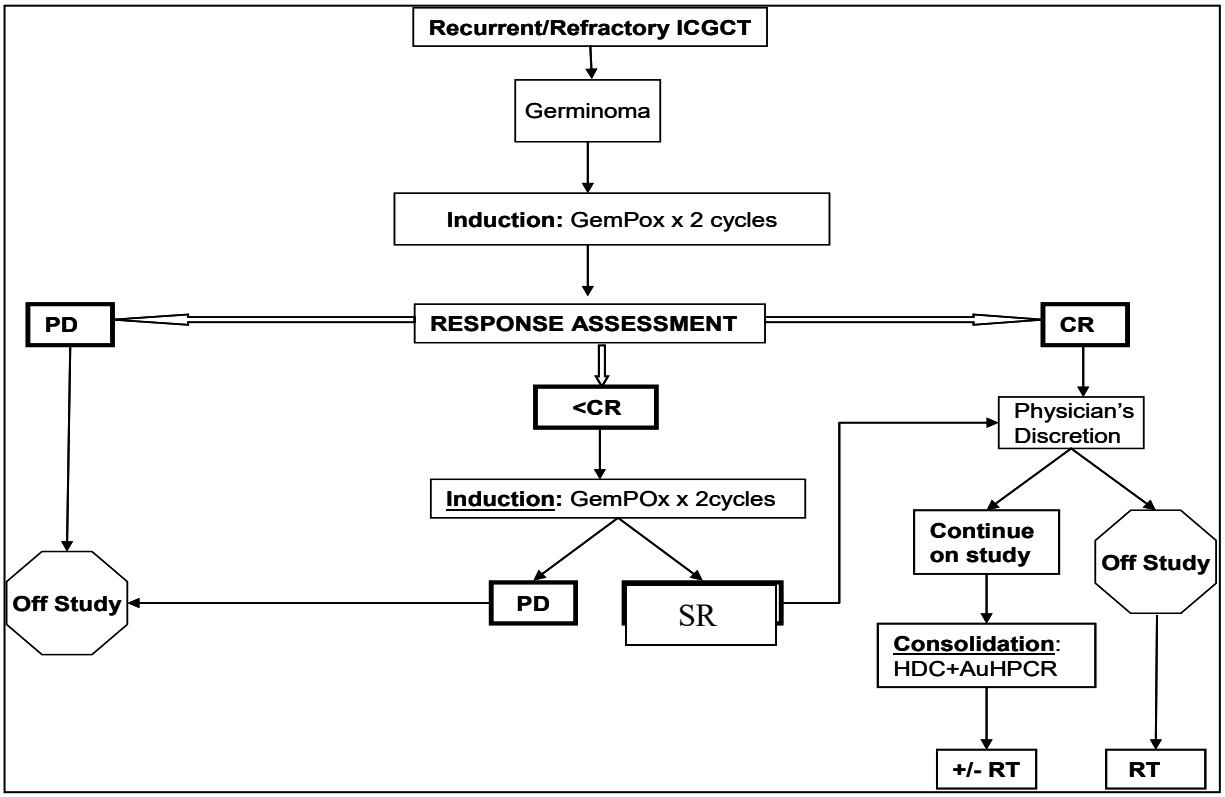


Figure 2: EXPERIMENTAL SCHEMA FOR PURE GERMINOMA

2.0 OBJECTIVES

2.1 Primary Objectives

2.1.1 To estimate response rate after at least two and up to four courses of induction chemotherapy with GemPOx regimen in patients with recurrent CNS MMGCT.

2.1.2 To estimate the rate of completion of induction chemotherapy and progression to high-dose chemotherapy (HDC) with autologous hematopoietic progenitor cell rescue (AuHPCR)

2.1.3 To assess the toxicity of GemPOx regimen in all patients with CNS GCT (pure germinoma and MMGCT).

2.2 Secondary Objectives

2.2.1 To correlate serum and cerebrospinal fluid (CSF) tumor marker (AFP and HCGβ) responses with radiographic response after two and/or four GemPOx cycles and also after HDC followed with AuHPCR.

2.2.2 To identify specific exosomal microRNAs in the CSF specific for recurrent CNS GCT at study entry and to determine if decrease/disappearance of such CSF MiRNAs correlates with radiographic and/or tumor marker documentation of response to induction and consolidation therapies, and correlates with event-free survival.

2.2.3 To assess the overall survival (OS) and event-free survival (EFS) of patients treated on the GemPOx induction regimen followed by the HDC and AuHPCR in patients with progressive or recurrent CNS GCT.

2.2.4 To determine the feasibility of peripheral hematopoietic stem cell mobilization with GemPOx induction regimen.

2.2.5 To evaluate the toxicity of HDC and AuHPCR following GemPOx induction.

3.0 BACKGROUND AND RATIONALE

3.1 Introduction on CNS Germ Cell Tumors (CNS GCT)

Patients with pure germinoma have a highly favorable prognosis with over an 80-90% cure rate using either irradiation alone or reduced dose and volume irradiation with modest chemotherapy.[1-14] However, patients with MMGCT, despite combined intensive chemotherapy and full dose craniospinal irradiation and focal boost, have a much poorer outcome, with reported survival rates ranging between 40 and 70 %.[1,10-13, 15]

There are very few studies that have addressed the treatment of patients with recurrent CNS germ cell tumors (GCT), largely due to the rarity of this disease.[16-18] High salvage rates using irradiation and chemotherapy are achieved for pure germinomas that were initially treated with chemotherapy alone.[16] However, sustained responses to the commonly used salvage regimens are difficult to achieve when relapses occur following combined chemotherapy and radiation therapy.[19] The survival of patients who experience relapse after both modalities of therapy, or those who do not respond to initial treatment, is very poor. Promising results have been published in case series incorporating novel salvage regimens with high dose, marrow ablative chemotherapy after achieving minimal residual tumor.[20, 21] In order to achieve a state of minimal residual tumor prior to a single cycle of myeloablative chemotherapy and AuHSCR, it is imperative that new drugs and drug combinations be evaluated that will have the best chance of achieving such tumor response.

The combination of gemcitabine, paclitaxel and oxaliplatin has been shown to be effective in recurrent systemic GCT arising outside the CNS.

3.2 Rationale for Gemcitabine (Gem)

In a phase II trial conducted at Indiana University, 20 patients with recurrent or progressive systemic GCT (13 patients were treated with three prior regimens and 13 patients were platinum refractory) received single agent gemcitabine.[22] Three (15%) out of 20 patients showed an objective response; including one complete response (CR). Three additional patients achieved a minor radiographic or tumor marker response. Gemcitabine was well tolerated with only one patient with grade 3 nausea and six patients with grade 3 leucopenia. In a phase II German trial of 31 patients with recurrent systemic GCT (22 patients had recurrence after HDC with AuHSCR), six patients (19%) responded favorably to gemcitabine alone, including two who experienced marker normalization and four who had a 75% decline in tumor markers.[23]

3.3 Rationale for Paclitaxel (P)

Preclinical studies of paclitaxel have demonstrated cytotoxicity in a non-seminomatous GCT cell line and in nude mouse xenografts.[24, 25] In a phase II clinical trial conducted at Memorial Sloan-Kettering Cancer Center, patients with recurrent and/or progressive testicular GCTs were treated with single agent paclitaxel.[26] Eight (26%) of 31 patients achieved an overall response. Responses were noted in those who had failed to respond to vinblastine, ifosfamide and cisplatin and in men with poor prognostic features, including mediastinal primary site and with incomplete responses to prior cisplatin therapy. Similar results were seen in a phase II German trial, in which 24 patients with poor prognostic GCTs achieved 25% response rate to single agent paclitaxel.[27] In addition, five patients (21%) displayed stabilization. The median duration of responses to paclitaxel was 8 months.

3.4 Rationale for Oxaliplatin (Ox)

Oxaliplatin, a third-generation platinum compound, is more effective than cisplatin and exhibits similar and greater cytotoxicity in several human tumor cell lines.[28] In comparison with cisplatin, oxaliplatin exhibits a favorable toxicity profile with a substantially lower rate of nephrotoxicity, ototoxicity and myelosuppression.[29, 30] *In vitro* data on non-seminomatous germ cell lines indicate incomplete cross-resistance between cisplatin and oxaliplatin, providing the rationale for the evaluation of oxaliplatin in cisplatin-refractory patients.[(31)] Additionally, the dose limiting toxicity, maximum - tolerated dose and adverse effect profile of oxaliplatin in pediatric patients are similar to those observed in adults.[32, 33] The Pediatric Brain Tumor Consortium conducted a phase II study of oxaliplatin in 43 children with recurrent malignant embryonal brain tumors and reported minimal toxicity and good tolerance to paclitaxel in children.[34] The German Testicular Cancer Study Group investigated the response of oxaliplatin in 32 patients with systemic GCT who were refractory to cisplatin or relapsed after HDC plus AuHSCR. Overall, four patients (13%) achieved a partial response (PR) and two patients achieved disease stabilization.[35]

3.5a Rationale for Paclitaxel and Oxaliplatin Combination

When paclitaxel was combined with oxaliplatin in the treatment of patients with systemic germ cell tumors who had failed cisplatin-based chemotherapy, 6% of the patients had a partial response and 34% of the patients had stabilization of their disease.[60]

The major toxicity with this combination was myelosuppression. Grade II sensory neurotoxicity was seen in 8/27 patients. No grade III or grade IV neurotoxicity was observed in this clinical trial demonstrating that paclitaxel and oxaliplatin combination is feasible and well tolerated.

3.5b Rationale for Gemcitabine and Paclitaxel Combination

A combination of gemcitabine and paclitaxel was evaluated in a phase II trial for patients with recurrent systemic GCT who recurred after receiving three prior regimens, some having undergone HDC plus AuHPCR.[36] Six (21.4%) of 28 patients responded, including three CRs. Two of the complete responders were continuously without disease at 15 and 25 months. Toxicity was primarily marrow suppression but was manageable, with only a single case of neutropenic fever. A phase II study was conducted at Indiana University of 32 patients with systemic GCT who had progressed after cisplatin combination chemotherapy and subsequent HDC with tandem transplantation. [37] Ten (31%) of the 32 patients achieved objective responses, of whom six were complete responders; four of these six (12.5%) were continuously disease free at 20, 40, 44 and 57 months from the start of the combined gemcitabine and paclitaxel therapy, respectively.

3.5c Rationale for Oxaliplatin and Gemcitabine Combination

The combination of gemcitabine and oxaliplatin yields excellent tolerability and predictable pharmacokinetics.[38] In a phase II study with a combination of oxaliplatin plus gemcitabine in 35 heavily pre-treated men with recurrent systemic GCT- three patients attained a CR, two patients attained a marker negative PR, and 11 patients attained tumor marker PRs, resulting in an overall response rate of 46%.[39] Major toxicity consisted mainly of myelosuppression. The combination of oxaliplatin and gemcitabine has been evaluated in several other small phase II trials, demonstrating similar outcomes.[40, 41]

3.5d Rationale for Combining Paclitaxel, Gemcitabine and Oxaliplatin (GemPOx)

Based on the series of the above consecutive phase II trials, the German group conducted a multi-center phase II clinical trial with combination of the gemcitabine, oxaliplatin and paclitaxel in patients who were either cisplatin refractory or multiply relapsed systemic GCT after HDC.[42] Of 41 patients, 5% achieved CR, 34% achieved tumor marker negativity, and 12% tumor marker partial responses, resulting in an overall response rate of 51%. In five responding patients, a complete tumor resection was feasible after the end of chemotherapy, resulting in an overall CR rate of 17%. After a median follow-up of 5 months (range 0-20), 15% of the patients remained in CR after the gemcitabine, oxaliplatin and paclitaxel chemotherapy with or without residual tumor resection, with median response duration of 8 months (1 to 17+). The major toxicities were leucopenia (grade 3) in 15%, anemia in 7% and thrombocytopenia in 49% of the patients.

3.6 Rationale for HDC and AuHPCR

Alkylating agents have been shown to be active against both CNS and systemic GCTs.[19] Thiotepa can cross the blood brain barrier extremely efficiently.[43] Dose response effects have been suggested for carboplatin and etoposide in patients with systemic GCT.[45, 46] The combination of carboplatin, etoposide and thiotepa has been used to treat malignant brain tumors and the combination has proven to be well tolerated.[44]

Modak *et al*. has assembled the largest experience with thiotepa-based HDC regimens followed by AuHSCR in the treatment of high-risk patients with recurrent CNS GCTs, many of whom had experienced multiple prior relapses of disease.[20] With a median follow-up of 35 months, seven of the nine patients with recurrent germinomas were alive, while four of the 12 MMGCTs patients were alive. Of the eight patients who achieved a CR with salvage protocols before consolidation with HDC, five survived without assessable disease six to 48 months after HDC. The French Society of Pediatric Oncology (SFOP) reported on 20 patients with recurrent ICGCT (13 MMGCT, 7 germinomas) who underwent HDC with AuHPCR using a conditioning regimen of etoposide and thiotepa; 16 were in first relapse, two in second relapse, two with refractory disease and 20 having received carboplatin based chemotherapy as part of their front line therapy prior to a recurrence. [(21)] Nine patients treated on this study had a complete response and nine achieved a partial response and only two patients had progression of their disease. At a median follow-up of 29 months, 16 patients were reported alive; 13 were in continuing complete remission (four with germinoma and nine with MMGCT). In a study conducted by the European Group for Blood and Marrow Transplantation[47] salvage HDC was utilized in 23 patients with extragonadal GCTs including nine patients with CNS GCTs. Twenty-two patients had MMGCT and one had germinoma. Complete responses were achieved in 16 of the 23 patients (70%). At a median follow-up of 66 months, 11 patients (48%) were reported disease- free of whom three patients (33%) had CNS GCT.

Reports from the two studies (Modak *et al.*[20] and SFOP[21]) have shown that the survival rate in patients with relapsed CNS GCT and especially with MMGCT is improved with the treatment strategy of HDC and AuHPCR when these patients are in CR prior to HDC.

3.7 Rationale For Evaluation of Cerebrospinal Fluid (CSF) exosomal microRNAs (MiRNAs)

More accurate tests to objectively determine the persistence of residual tumor, such as that afforded by persistence of specific tumor-related miRNAs are needed to tailor and optimize therapies. Exosomes are endosomally-derived membrane vesicles that are released from both healthy and tumor cells, including germ cell tumors arising both within the brain and beyond. Packaged within exosomes are microRNAs (miRs), some of which are tumor specific oncomiRs that are up-regulated in the presence of certain cancer cells; specific cancers have distinct miR profiles. Brain tumor related exosomes, containing their miR cargo, eventually reach the CSF, so that changes in the amount of miR burden in the brain is reflected in measurements of miRs in the CSF, providing significant and direct information on the presence or absence of tumor cells within the brain. Therefore, exosomal miR profiles in the CSF may serve as biomarkers of tumor persistence or recurrence or elimination following therapy.

Two groups have independently reported upon miR profiles in CNS germ cell tumors (Terashima et al Br. J. Neurosurg. (abstr) 2013), or intra-and extra-CNS GCT (Murray et al, Br. J. Neurosurg. (abstr) 2013) showing that miR 371-375 and miR-302a isolated from the CSF of GCT patients are highly up-regulated prior to treatment, and decreased following treatment, with specific miRs associated with specific germinoma and non-germinomatous histologic sub-types.

We hypothesize that specific CSF miRNA will prove to be accurate markers for tumor presence and predictors of response to therapy, with normalization being associated with improved progression-free survival in patients under treatment for recurrent central nervous system (CNS) germ cell tumors (GCT). The goal of the proposal is to prove this hypothesis within the context of an ongoing prospective multi-center trial of uniform treatment for patients with recurrent CNS GCT.

4.0 PATIENT ELIGIBILITY AND STUDY ENTRY

Important note: **The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required as eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification.**

4.1 Study Enrollment

4.1.1 IRB Approval

Protocol must be approved by the treating institution's Institutional Review Board (IRB) and on file at Nationwide Children's Hospital

4.1.2 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is to start must be no later than 42 days from the time of recurrence and within 7 days from enrollment.

4.2 Patient Status

4.2.1 Age

No age limit

4.2.2 Diagnosis

Histological Diagnosis

CNS GCT including pure germinoma and MMGCT. Patients with histologically proven germinoma and MMGCT, including endodermal sinus tumor (yolk sac tumor), embryonal carcinoma, choriocarcinoma and mixed germ cell tumor will be eligible for the study. Patients with mature/immature teratoma who have tumor marker elevations are eligible on this study. Patient with ONLY mature and/or immature teratoma are *ineligible* in the absence of the tumor marker elevations.

Cytology and Tumor Markers

- Lumbar CSF must be assayed for cytology, alpha fetoprotein (AFP) and beta human chorionic gonadotrophin (HCGβ). A quantitative serum determination of AFP and HCGβ should be performed at the time of the lumbar CSF assay.
- For the diagnosis of pure germinoma, HCGβ (serum and CSF) must be ≤ 100 mIU/ml, serum AFP must be ≤ 10 IU/l (ng/ml) and ≤ institutional norm and initial CSF AFP≤ 2 IU/l (ng/ml) and ≤ institutional norm with histologically proven diagnosis of germinoma at diagnosis or subsequent relapse.
- For histologically unconfirmed MMGCT, serum and/or CSF tumor markers of HCGβ >100 mIU/ml or any elevation of above AFP>10 IU/L (ng/ml) and/or above institutional norm in the serum and CSF AFP≥2 IU/L (ng/ml) and/or institutional norm.

- Patients with ***no*** elevations of serum and/or CSF HCGβ and AFP ***must*** have histological diagnosis of malignant GCT or germinoma.

4.2.3 Disease Status:

Patient must either have recurrence of CNS GCT or should be refractory to initial therapy.

4.2.4 Disease Evaluation

4.2.4.1 Diagnostic Imaging

a) MRI scans of the brain and spine must be completed within 21 days prior to patient registration. All MRI scans should be with and without gadolinium.
b) All patients who do not have surgery performed must have MRI scans obtained prior to induction.
c) All patients who have surgery performed must have a cranial MRI pre-operative and post-operative (should be done within 72 hours of surgery or within 21 days following surgery).
d) A MRI of the spine is required within 10 days prior to or at least 10 days after surgery.

4.2.4.2 Tumor Markers

a) Serum HCGβ and AFP levels must be assessed within 7 days prior to registration.
b) Patient must have lumbar CSF for cytology, protein, AFP and HCGβ within 7 days prior to registration.

4.2.5 Performance Status

Have a Karnofsky performance status greater than or equal to 50 for patients aged 16 years or older and a Lansky performance status greater than or equal to 50 for patients less than 16 years old.

4.2.6 Life Expectancy:

Must be $\geq$ 8 weeks.

4.2.7 Prior Therapy

4.2.7.1 Chemotherapy

a) Must not have received cytotoxic chemotherapy within 14 days of entry on to this study.
b) Patient must not have received any prior marrow-ablative chemotherapy and autologous hematopoietic cell transplant.
c) Patient must have not received gemcitabine, oxaliplatin and/or paclitaxel chemotherapy agents.

4.2.7.2 Biologic Agent

Must not have received any biological modifier within 14 days of entry on to this study.

4.2.7.3 Radiation Therapy (RT)

At least 4 weeks for focal RT or ≥ 6 weeks for craniospinal RT must have elapsed prior to study entry.

4.2.7.4 Surgery

Patient must have recovered from the surgery.

4.2.8 Concomitant Medications

- Corticosteroid therapy and endocrine replacement therapy (L-thyroxine, testosterone, estrogen, DDAVP) are permissible. Any patient already receiving human growth replacement therapy should discontinue this prior to commencing chemotherapy, and should not restart until 3 years from diagnosis.

- Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary.

- Concomitant use of any enzyme inducing anticonvulsants is not allowed.

4.3 Organ Function Requirements

4.3.1 Adequate Bone Marrow Function Defined As:

- Absolute neutrophil count (ANC) greater than or equal to 750/mm^3
- Platelets (Plts) greater than or equal to 75,000/mm^3 (transfusion independent)
- Hemoglobin (Hgb) greater than 8.0 g/dL (may have packed red blood cell (PRBC) transfusion)

4.3.2 Adequate Liver Function Defined As:

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x institutional upper limit of normal for age
- Total bilirubin ≤ 2 x institutional upper limit of normal for age
- Liver function test must be obtained within 14 days prior to registration.

4.3.3 Adequate Renal Function as Defined As:

- Patients must have adequate renal function defined as < 1.5x normal serum creatinine as adjusted for age:

Age	Maximum Serum Creatinine (mg/dL)
< 5 years	0.8
> 5 and < 10 years	1.0
> 10 and < 15 years	1.2
> 15 years	1.5

- Or a calculated or measured creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73m^2 obtained within 14 days prior to registration.

4.4 Pregnancy/Contraception

Patients who are pregnant or breast-feeding are not eligible. Nursing mothers must agree not to breastfeed during therapy. Females of childbearing potential must practice an effective method of birth control while participating in this study and for those who have achieved menarche, must have a negative pregnancy test prior to study entry.

4.5 Regulatory

4.5.1 All patients and/or their parents or legal guardians must sign a written informed consent.
4.5.2 All institutional and FDA requirements for human studies must be met.

4.6 Exclusion Criteria

4.6.1 Patients with CNS GCTs who are newly diagnosed are excluded from the study.
4.6.2 Patients with the diagnosis of mature or immature teratoma in the absence of tumor marker elevations are excluded from the study.
4.6.3 Patients who are pregnant or breastfeeding are excluded from the study.
4.6.4 Patients who have received previously a high dose chemotherapy regimen and autologous transplant are excluded from this study.
4.6.5 Patients who have received gemcitabine, oxaliplatin and/or paclitaxel are excluded from this study.

5.0 TREATMENT PLAN

5.1 Induction Treatment Plan:

- All patients with CNS GCT after enrollment to this study will receive two cycles of induction chemotherapy regimen GemPOx. Only patients who have failed to achieve a sufficient response (SR) and do not have progression of their disease will receive two additional cycles with a maximum of four induction cycles.
- A cycle is defined as 14 days unless there is a delay in bone marrow recovery. No more than 28 days of delay will be allowed when leukapheresis is planned in between induction cycles. Leukapheresis is allowed ONLY after two induction cycles. For details on Leukapheresis, see section 5.2. For details on delay in beginning a cycle due to prolong myelosuppression, see section 5.1
- Each cycle will begin when ANC $\geq$ 750/mm^3 and platelets $\geq$ 75,000/mm^3. Please see section 9.1 for additional monitoring that is required prior, during and following each induction cycle.
- Treatment regimen consists of paclitaxel 170mg/m^2 IV over three hours followed by gemcitabine 800mg/m2 IV 10mg/ m^2/min over 1 hour and oxaliplatin 100/m^2 IV over 2 hours.

AGENT	DOSE	ROUTE/DURATION	DAYS	INTERVAL
Paclitaxel	170mg/m^2	IV over 3 hours	D1	14 days
Gemcitabine	800mg/m^2	IV over 1 hour	D1	14 days
Oxaliplatin	100mg/m^2	IV over 2 hours	D1	14 days

- Further therapy for patients with **germinoma** who have achieved sufficient response either after two or four induction cycles will depend on the discretion of the treating physician. Physician can decide to continue the patient on this study to receive the consolidation phase or remove the patient from the study and treat him with radiation therapy.
- Patients with intracranial **MMGCT** who have achieved sufficient response either after two or four induction cycles will proceed on this study to receive the consolidation phase. After four cycles if patient has any residual disease (patients with PR or SD), a "second look surgery" will be strongly recommended. If CR is achieved following second-look surgery, they would proceed to consolidation phase.
- Patients with an increasing mass in the context of normal serum and CSF tumor markers should proceed to second-look surgery in order to evaluate for growing teratoma syndrome (GTS). If the patient does have GTS, complete removal of the mass is recommended. Patient can then continue therapy on this protocol following the surgery. For details on the diagnosis of GTS please see section 14.3.
- All patients developing PD (after excluding GTS) will be considered off study therapy.

5.1.1 Induction Chemotherapy Administration Guidelines

Patients should have double lumen venous catheter line to receive chemotherapy. Consideration should be given to placement of a tunneled leukapheresis-grade catheter to use for chemotherapy administration and peripheral hematopoietic stem cell collection. Institutional standards may take precedence for dilution of individual medications, hydration and antiemetics. The use of magnesium and calcium containing hydration solutions to decrease incidence of peripheral neuropathy is not encouraged.

Suggested Pre-chemotherapy Hydration: D5 0.45 Normal Saline to run at 125ml/m^2/hour until chemotherapy ready.

Hour – 30 minutes: **Suggested Pre-medications and Antiemetics**

Dexamethasone 0.5 mg/kg/dose IV 30 minutes prior to paclitaxel (maximum dose: 50 mg) and continue every six hours for 24 hours.

Ranitidine 1 mg/kg IV 30 minutes prior to paclitaxel x one dose (maximum dose: 50 mg).

Diphenhydramine 0.5-1 mg/kg IV 30 minutes prior to paclitaxel x one dose (max dose: 50 mg.

Antiemetics as per the choice of treating physician and institutional standards to be used.

- **Hour 0:** Paclitaxel 170 mg/m^2 in D5W (dose<100mg =150ml; ≥ 100mg=250ml) IV over 3 hours x 1 dose on day 1 only followed by:

- **Hour 3:** Gemcitabine 800 mg/m^2/dose in 250ml normal saline IV over 1 hour x 1 dose on day 1 only followed by:

- **Hour 4:** Oxaliplatin 100 mg/m^2 in 250ml D5W IV over 2 hours x 1 dose on day 1 only.

- **Hour 6:** Resume hydration with D5 0.45 Normal Saline to run at 125 ml/m^2/hour until discharge.

Antiemetics at any time are permissible during treatment and should be given as per the institutional policy. Replacement of serum electrolytes may be undertaken at any time during treatment.

***Note:** During oxaliplatin infusion patients can experience the feeling of difficulty swallowing, shortness of breath, shortness of breath, jaw spasm, abnormal tongue sensation and feeling of chest pressure. This has been reported rarely (<5%). It generally starts within hours of oxaliplatin infusion and often occurs upon exposure to cold. Avoiding exposure to cold helps to prevent this adverse reaction. Future oxaliplatin infusions may be given over a longer time frame to help reduce the incidence.

The following are the safety tips that should be advised to each patient receiving this treatment:

While receiving treatment with oxaliplatin advice:

- Cover the skin, mouth and nose if he/she must go outside in cold temperatures and do not breathe deeply when exposed to cold air.
- Do not drink cold drinks or use ice cubes in drinks during and at least for two days following oxaliplatin administration.
- Do not put ice or ice packs on his/her body during and at least for two days following oxaliplatin administration.
- Cover self with a blanket while she/he is receiving oxaliplatin infusion.
- Do not take things from the freezer or refrigerator without wearing gloves.

- Drink fluids warm or at room temperature and always drink through a straw.
- Do not use ice chips if she/he has nausea or a sore mouth.

5.1.2 Duration of Induction Treatment:

- Patients will continue treatment every 2 weeks until at least 2 cycles have been administered.
- Only, patients who have failed to achieve a sufficient response and do not have progression of their disease will receive two additional cycles with a total of four induction cycles.
- Patient is taken off protocol therapy if patient develops tumor progression at any time during the induction phase.

5.1.3 DOSE MODIFICATIONS DURING INDUCTION CHEMOTHERAPY

- Grades I and 2 toxicities should be managed symptomatically, if possible, and treated without reduction in the chemotherapy doses. If toxicities are greater than Grade 2, treatment should be withheld (except for anemia or neuropathy or as specifically indicated below) until recovery to Grade I (or baseline, if baseline was > Grade I).

- Dose modifications for the next cycle and additional cycles are based on day 15 complete blood count with differential and toxicity work sheet unless the patient develops cytopenia associated infection or bleeding during the prior cycle (see below) or requires hospital admission at which time a toxicity assessment should be undertaken and complete blood count obtained.

5.1.3.1 Myelosuppression:

To begin each cycle of induction therapy the following criteria must be met: ANC $\geq$ 750/mm^3 and platelets $\geq$ 75,000/mm^3. In the event a patient does not meet the criteria for re-treatment, then a maximum of 14 days delay is allowed. After a 14-day delay the study PI should be contacted. If the patient has a delay for 7 days in beginning the next cycle due to low blood counts then Filgrastim (G-CSF) (5 mcg/kg/day Subcutaneously or IV) should be administered 24 hours after the chemotherapy for subsequent cycles. G-CSF should be continued until ANC is $\geq$1000/mm^3 and discontinued at least 48 hours prior to initiation of the next cycle. If there is a delay in beginning the next cycle for more than 7 days due to delay in the bone marrow recovery despite the administration G-CSF, the doses of oxaliplatin, gemcitabine and paclitaxel should be *reduced by 25%* for all subsequent cycles.

5.1.3.2 Hepatotoxicity:

If the ALT levels are $\geq$ 10x upper limit of normal (ULN) and/ or total bilirubin is > 2mg/dl before the second cycle of treatment, delay start of chemotherapy for 7-14 days. If the liver function has not returned to normal, (after a 14-day delay) the study PI should be contacted.

5.1.3.3 Nephrotoxicity:

If there is an indication of worsening renal function after any course of treatment, a creatinine clearance or GFR should be determined. If creatinine clearance is <70 ml/min/1.73m^2, delay start of chemotherapy for 7 days and re-check the creatinine clearance. If the kidney function has not returned to normal (after a 14-day delay) the study PI should be contacted.

5.1.3.4 Stomatitis:

If Grade 3 and 4 stomatitis occurs, hold chemotherapy until recovery to Grade <1.

5.1.3.5 Paclitaxel Hypersensitivity reactions:

Treatment shall be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for Paclitaxel hypersensitivity reactions.

Hypersensitivity Treatment Guidelines:

Grade 1:

- Consider decreasing the rate of paclitaxel infusion until recovery from the symptoms; closely monitor patient.
- Resume paclitaxel at the planned initial rate after symptoms resolve on that day of treatment.

Grade 2:

- Interrupt paclitaxel infusion immediately.
- Give diphenhydramine with or without hydrocortisone; monitor patient until symptoms resolve.
- Resume infusion after recovery of symptoms; depending on the physician's assessment of the patient, infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate.
- Depending on the intensity of the reaction observed, additional oral or IV pre-medication with an antihistamine should also be given for subsequent cycles of treatment, and the rate of paclitaxel infusion should be decreased initially and then increased back to the recommended rate gradually depending on the physician's assessment of the patient.

Grade 3:

- Immediately discontinue paclitaxel infusion.
- Give diphenhydramine with or without hydrocortisone and or epinephrine as needed; monitor patient until resolution of symptoms.
- Resume infusion after recovery of symptoms on that day of treatment; depending on the physician's assessment of the patient, infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate.

- Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for subsequent induction treatment cycles. The rate of infusion should be decreased initially and then increased back to the recommended one hour if symptoms have resolved.

Grade 4:

- Infusion should be DISCONTINUED. Patient is taken off protocol therapy.

5.1.3.6 Peripheral Neuropathy:

Neuropathic symptoms and signs: Patients may be treated if they have grade 2 neuropathy but dose delay will be at the physician's discretion and dose reduction should not be undertaken. For grade 3 or greater neuropathy, all drugs must be held until resolution to grade 2, at which time the patient should have a *25% reduction in doses of oxaliplatin and paclitaxel*. Dose modification will NOT be undertaken for transient neuropathic symptoms during the cycle that have resolved by day one of the subsequent cycle.

OXALIPLATIN DOSE MODIFICATIONS FOR NON-CTC NEUROLOGICAL TOXICITY			
Toxicity	**Duration of toxicity**		**Persistent[1]**
	1-7 days	**>7days**	**Between Cycles**
Paresthsias/dysesthesias			
Grade 1: Paresthesias/dysesthesias[2] of short duration that resolves and do not interfere with function.	No change	No change	No change
Grade 2: Paresthesias/dysesthesias[2] interfering with function, but not ADL	No change	No change	25% dose reduction
Grade 3: Paresthesias/dysesthesias[2] with pain or with functional impairment that also interfere with ADL	1st time: 25% dose reduction 2nd time: 50% dose reduction	1st time: 25% dose reduction 2nd time: 50% dose reduction	Stop infusion
Grade 4: Persistent Paresthesias/dysesthesias that are disabling or life threatening	Stop infusion. Patient is taken off protocol therapy.	Stop infusion. Patient is taken off protocol therapy.	Stop infusion. Patient is taken off protocol therapy.
Pharyngolaryngeal Dysthesias (Investigator discretion used for grading):			
Grade 0 = none Grade 1 = mild	No change	Increase duration of infusion to 6 hours	Increase duration of infusion to 6 hours

Grade 2 = moderate	• Stop oxaliplatin infusion. • Administer benzodiazepine and give patient reassurance. • At the discretion of the investigator, the infusion can be restarted at 1/3 the original rate of infusion**.**
Grade 3 = severe	

1 = Not resolved by the beginning of the next cycle.
2 = May be cold induced.
ADL = Activities of daily living

5.2 Collection of Peripheral Hematopoietic Progenitor Cells (HPCs)

5.2.1 Insertion of indwelling venous access catheter:

In children without an appropriate double-lumen leukapheresis-grade catheter in place, leukapheresis may be accomplished through a percutaneously placed temporary leukapheresis-grade catheter, which is then removed following completion of the leukapheresis.

5.2.2 Priming with G-CSF:

If the decision is made to harvest peripheral HPC prior to initiation of chemotherapy, then for three days prior to undergoing peripheral HPC leukapheresis, patients will receive G-CSF at a dose of 10-16 mcg/kg given as a daily subcutaneous injection, or 16 mcg/kg per day given as twice-daily intravenous injections. G-CSF will be discontinued following the last day of leukapheresis.

5.2.3 Timing for Leukapheresis:

Collection of peripheral HPC should be planned ONLY after patients have received two induction cycles. Peripheral HPC can be collected after completing second induction cycle or before beginning third or fourth induction chemotherapy cycles.

It is best harvested upon recovery from the induction chemotherapy. As soon as the absolute neutrophil count (ANC) is observed to be rising, the G-CSF dosage is increased to 10-16 mcg/kg per day as subcutaneous injections. G-CSF will be discontinued following the last day of leukapheresis.

5.2.4 Leukapheresis:

Leukapheresis (for the collection of peripheral blood hematopoietic progenitor cells) will be performed using a continuous flow cell separator according to the procedure manual with adaptations for small children as outlined below. In children without an appropriate double-lumen leukapheresis-grade catheter in place, this may be accomplished through a percutaneously placed temporary leukapheresis-grade catheter, which is then removed following completion of the leukapheresis.

For patients primed with G-CSF alone, leukapheresis will begin following the fourth day of G-CSF. Following each leukapheresis, the cells will be cryopreserved as described in Section 5.2.5.

Prior to freezing, an aliquot of each collection will be analyzed for cell count and immunophenotype. The target for the leukapheresis will be 5 x 10^6 CD34+ cells/Kg, with the goal of infusing no less than 2 x 10^6 CD34+ cells/Kg and no more than 10 x 10^6 CD34+ cells/kg.

For very small patients, the leukapheresis procedure established for adults will be modified. During the procedure, a set volume of blood is contained in the tubing and apparatus. For larger children and adults, this represents less than 10% of their total blood volume and is usually well tolerated. However, in very small children, the extracorporeal blood volume may be >10% of their total blood volume and this may cause clinically significant hypovolemia. For patients for whom the extracorporeal blood volume is >10% of their total blood volume, the machine will be primed with irradiated packed red blood cells (PRBC).

5.2.5 Peripheral HPC Processing:

Peripheral HPCs should be processed, frozen and stored in a Hematopoietic Cell Cryopreservation Laboratory per using standard institutional procedures.

5.3 Guidelines for Proceeding to Consolidation with High Dose Chemotherapy (HDC)

Following recovery from the final cycle of induction chemotherapy, the patient will undergo an extent of disease evaluation (see section 9.1).

- Following completion of induction chemotherapy, if there is no evidence of obvious residual tumor, both on imaging studies and by serum and CSF tumor markers, on extent of disease evaluation, patients will proceed directly to the consolidation HDC.

- Following the extent of disease evaluation upon completion of induction chemotherapy, if there is radiographic evidence of residual tumor on extent of disease evaluation, then a "second-look" surgical procedure should be performed. After second–look surgery all patients will undergo repeat extent of disease evaluation. Following the extent of disease evaluation and recovery from the surgery, all patients with CR/CRU/VGPR/PR/SD will proceed to consolidation HDC.

- Following completion of induction chemotherapy, if there is radiographic evidence of residual tumor on extent of disease evaluation, which cannot be grossly resected, then the patient will proceed directly to consolidation HDC.

- If there is evidence of tumor progression at any time during the induction chemotherapy or at the extent of disease evaluation following the completion of induction chemotherapy, either by imaging or tumor marker evaluation in the serum or CSF, then the patient is considered to have failed the protocol and will discontinue further study-prescribed treatment.

5.4 Consolidation HDC Treatment Plan

DAY	DRUGS	DOSE	ROUTE/DURATION
D -8 to -6	Carboplatin	500 mg/m^2 or calculated by Calvert formula (the smaller value of the two will be utilized)	IV over 4 hours
D -5 to -3	Thiotepa	300mg/m^2 or 10mg/Kg (if <36 mos old)	IV over 3 hours
	Etoposide	250mg/m^2 or 8.3mg/Kg (if < 36 mos old)	IV over 3 hours
D -2 to -1	None	None	None
D 0	Autologous Hematopoietic Progenitor Cell Rescue		

Following completion of the post-induction extent of disease and organ function evaluations, (see section 9.1), patients will undergo consolidation HDC not later than four weeks from the end of the last induction cycle. The treatment is as follows:

5.4.1 Days -8, -7 and –6:

Carboplatin will be infused intravenously over four hours daily for three days beginning day -8. The daily dose of Carboplatin will be derived from the creatinine clearance or GFR result measured prior to **each** dose of Carboplatin. The dose is calculated using the Calvert formula. This formula was derived to give the same systematic exposure (AUC) to carboplatin for patients with varying renal function. Total body carboplatin clearance is the sum of the non-renal clearance plus renal clearance.

For the most part, the non-renal clearance is related to body weight. The renal clearance is directly proportional to the raw creatinine clearance (NOT adjusted to 1.73 m^2). The dose equals the AUC times total body clearance.

Dose (mg) = desired AUC (mg/ml/min) x body clearance

Dose (mg) = AUC x (renal clearance + non-renal clearance)

Patients < 10 years of age:

Daily dose = AUC x (raw creatinine clearance + (body wt. x 0.36)

Patients 10 years of age or greater:

Daily dose = AUC x (raw creatinine clearance + 25)

For a dose of 500 mg/m^2 with normal renal function, the desired AUC is approximately 7 mg/ml/min.

Caveats:

- The raw creatinine clearance must be used or the patient will be overdosed by a factor of 1.73/BSA. (Up to 3.5 times 0.5m^2). Two people should check the dose and it should be compared to the dose calculated by BSA.
- The dose derived from the calculation is the total dose in milligrams, not the dose per m^2.

- Patients with supra-normal creatinine clearance will not get a higher dose than that calculated at a dose of 500 mg/m^2 or 16.7 mg/kg for children < 3 years of age. The dose of Carboplatin will be calculated using both the Calvert formula and surface area (500 mg/m^2 or 16.7 mg/kg) and the lower of the two will be used.
- While hyperhydration is not required with carboplatin administration, patients should be assured at least maintenance fluid intake, either intravenously or orally, with replacement of emesis losses, to avoid dehydration and possible acute renal insufficiency.

5.4.2 Days -5, -4 and –3:

Thiotepa 300 mg/m² or 10 mg/kg (if patient age <36 months) should be infused intravenously over three hours to start approximately 24 hours after completion of the last dose of Carboplatin and will be repeated daily for three days at approximately 24 hour intervals.

Thiotepa diluted to <1 mg/ml is stable for 8 hrs or less depending on final concentration. Concentrations >1 mg/ml are stable for 24 hrs at room temperature. This may be significant if a diluted thiotepa dose is made early in the day and not administered until late in the afternoon.

Etoposide (VP-16) 250 mg/m² or 8.3 mg/kg (if patient age < 36 months)) should be infused intravenously over three hours in 0.9% normal saline (NS) to start immediately upon completion of the Thiotepa infusion each day. The duration of the etoposide may be extended in the event that hypotension develops at the faster infusion rate. The infusion time is rounded up to the nearest 30-minute period. The final concentration is not to exceed 0.6 mg/ml. If etoposide is concentrated to more than 0.5 mg/ml it is stable for 8 hrs or less, depending on the final concentration (i.e. 0.6 mg/ml = 8 hrs, 1 mg/ml = 2 hrs stability).

5.4.3 Therapy Scheme:

Day -8: Carboplatin, as calculated from AUC of 7 approx. hour 0
Day -7: Carboplatin, as calculated from AUC of 7 approx. hour 24
Day -6: Carboplatin, as calculated from AUC of 7 approx. hour 48
Day -5: Thiotepa 300mg/m² or 10 mg/Kg (if age < 36 mos) approx. hour 72
Day -5: Etoposide 250mg/m² or 8.3 mg/Kg (if age < 36 mos) approx. hour 75
Day -4: Thiotepa 300mg/m² or 10mg/Kg (if age <36 mos) approx. hour 96
Day -4: Etoposide 250mg/m² or 8.3 mg/Kg (if age < 36 mos) approx. hour 99
Day -3: Thiotepa 300mg/m² or 10mg/Kg (if age < 36 mos) approx. hour 120
Day -3: Etoposide 250mg/m² or 8.3 mg/Kg (if age <36 mos) approx. hour123
Day -2: Rest
Day -1: Rest
Day 0: Re-infusion of peripheral HPCs approx. hour 200

5.4.4 Peripheral HPC Re-infusion Day 0:

Peripheral HPCs will be thawed and re-infused approximately 72 hours following completion of the last dose of chemotherapy. Patients should be adequately hydrated prior to the HPC re-infusion.

The previously cryopreserved peripheral HPCs should be rapidly thawed in a 37^{o}C water bath and re-

infused through a central venous catheter. If the dose of dimethylsulfoxide (DMSO) exceeds 1 gm/kg/day then consideration should be given to infusing the peripheral HPCs in two aliquots over two days.

5.4.5 Post-HPC Re-infusion Hematopoietic Growth Factor (G-CSF) Therapy:

Beginning day +1 post-HPC reinfusion, patients should receive G-CSF at a dose of 5 mcg/kg IV or subcutaneously once daily until the ANC is>1,000/mm^3 for three consecutive days or as per the treating physician's preference. If the ANC is not >500/mm^3 by Day +21 post-HPC re-infusion, then the dose of G-CSF should be doubled. Additional autologous HPCs, if available, may also be infused at this time.

5.5 Radiation Therapy

Radiation therapy can be given after the recovery from the consolidation phase in patients with intracranial germinoma or MMGCT. Patient with ONLY germinoma can receive radiation therapy after induction therapy without undergoing the consolidation phase. The volume and the field of radiation therapy will be determined by the treating physician.

6.0 SUPPORTIVE CARE GUIDELINES DURING INDUCTION

6.1 Venous Access

Patients should have double lumen venous catheter line to receive chemotherapy. Consideration should be given to placement of a tunneled pheresis catheter to use for chemotherapy administration and peripheral HPC collection. During leukapheresis, in the absence of an appropriate double-lumen leukapheresis-grade catheter in place, a percutaneously placed temporary leukapheresis-grade catheter should be placed, which should be removed following completion of the leukapheresis procedure.

6.2 Antiemetics

Appropriate antiemetics should be administered prophylactically and as needed during chemotherapy. Corticosteroid use as an antiemetic should be avoided, if possible.

6.3 Use of Hematopoietic Growth Factor (G-CSF)

Routine use of G-CSF during induction is not recommended on this protocol. However, if the patient has a delay for 7-14 days in beginning the next cycle due to low blood counts then G-CSF should be administered (for details see section 5.1.3.1). Also, G-CSF is administered during induction cycle when leukapheresis is planned for peripheral hematopoietic stem cell harvest (for details see section 5.2). Additionally, G-CSF can be administered to patients with severe life threatening infections associated with neutropenia, at the discretion of the treating physician.

If G-CSF is administered during induction cycle, it should be noted on the study case report forms.

6.4 Blood Products

PRBCs should be given for symptomatic anemia or Hgb < 8 gm/dL. Platelets should be transfused for platelets <20,000-30,000 at any time. All blood products should be irradiated and leukoreduced. Blood products should be irradiated following the current Food & Drug Administration (FDA) guidelines found at: http://www.fda.gov/cber/gdlns/gamma.html. Investigators in Canadian institutions need to follow the Canadian Standards Association (CSA) standards for Blood and Blood Components CAN/CSA-Z902-04 issued in March 2004 and available at http://www.shopcsa.ca.

6.5 Febrile Neutropenia

Febrile neutropenia should be managed according to the local institutional guidelines. Measures may include laboratory testing, blood and urine cultures, and institution of broad-spectrum antibiotics.

6.6 Pneumocystis Jiroveci (Carinii) Prophylaxis

Patients who receive chemotherapy should be started on trimethoprim/sulfamethoxazole (TMP/SMZ) at 5mg/kg/day dosed 2-3x/week or per primary care institution protocol for Pneumocystis jiroveci (carinii) prophylaxis. TMP/SMZ administration can be ceased 4-6 months after therapy has been discontinued. Patients with TMP/SMZ allergy should be considered for treatment with dapsone or pentamidine (intravenously or inhaled).

6.7 Fungal prophylaxis

Appropriate antifungal prophylaxis therapy should begin upon starting protocol chemotherapy.

6.8 Nutritional Support

Any patient with greater than 10% weight loss from the baseline should begin nutritional supplementation. Nutritional support can be provided by enteric feeding or parenteral hyperalimentation. Use of appetite stimulants is also recommended.

6.9 Diabetes Insipidus

Tumors in the suprasellar or pineal areas may present with central diabetes insipidus (DI). Alternatively, patients may develop DI after neurosurgical intervention.[48] Central DI is defined as the inability to release vasopressin from the posterior pituitary in order to reabsorb free water at the renal collecting duct. DI manifests as, and is diagnosed by hyperosmolality (>300 mOsm/L) with simultaneous hyposthenuria (<300 mOsm/L). Patients will exhibit polyuria and nocturia, with a 24-hour urine output above 100 mL/kg/d. Those with an intact thirst mechanism will increase their fluid intake to maintain a normal serum osmolality. Those with an absent thirst mechanism (adipsia) may present with hypernatremia and severe dehydration. Diagnosis can be suspected by fasting the patient overnight and obtaining both first-void morning urine for specific gravity and osmolality along with a simultaneous blood specimen for sodium and serum osmolality. Inconclusive cases may require a water deprivation test, which should be performed in a Pediatric Clinical Research Center.

Treatment of DI requires chronic management with DDAVP, which can be administered in subcutaneous (4 µg/ml), intranasal (10 µg/0.1 ml), and tablet (100 µg, 200 µg) forms. This is best performed in conjunction with a pediatric endocrinologist.

During the entire treatment on this protocol, it is essential that fluid intake and output be carefully monitored in patients with DI. Placement of a Foley catheter is sometimes necessary for accurate measurement of urine output. In order to prevent renal dysfunction, a steady and increased urine output should be achieved by an appropriate DDAVP dosing schedule. This can be established in conjunction with a pediatric endocrinologist.

7.0 SUPPORTIVE CARE GUIDELINES DURING CONSOLIDATION

7.1 Post-Autologous HSC Re-infusion G-CSF Therapy

For details see Section 5.4.5.

7.2 Blood Product Support

For details see Section 6.4.

7.3 Pneumocystis jiroveci (Carini) Prophylaxis

All patients should receive the fixed combination of trimethoprim (5mg/Kg/day) and sulfamethoxazole (25mg/Kg/day) in divided doses from day -12 to day -3, either orally (if tolerated) or intravenously as prophylaxis for Pneumocystis carinii pneumonia. This should restart between day +50 and +70 when the platelet count is greater than 100,000/mm^3 and maintained for approx. 6 months at a dose of trimethoprim 5 mg/Kg/day and sulfamethoxazole 25 mg/Kg/day on 2 or 3 consecutive weekdays each week. Patients with a history of allergy to sulfonamides, or who's peripheral blood counts decline with exposure to TMP/SMZ or whose counts have not recovered by day +50 to +70, should receive pentamidine 4 mg/Kg IV per dose (maximum 300 mg); several regimens for this exist: one employs 4 doses intravenously given within a two week period or by inhalation for 5 doses within a two week period, and then once every 2 to 4 weeks intravenously or by inhalation, commencing on day +28. The dose of aerosolized pentamidine is 300 mg per dose for all patients $\geq$ 5 years of age.

7.4 Viral Prophylaxis

Patients with clinical or serologic history of herpes simplex virus or varicella-zoster virus infections should receive intravenous acyclovir 250 mg/m^2 IV every 8 hours, starting from Day +1 until discharge from the hospital. After discharge, patients should receive oral acyclovir 250 to 400 mg/m^2 orally three times daily until day +30.

7.5 Fungal Prophylaxis

Appropriate antifungal agents should be used throughout consolidation, such as fluconazole, clotrimazole troches 10 mg three times daily or nystatin 5 mL swish and swallow 3 to 4 times daily, until mucositis resolves and ANC is greater than 500/mm^3.

7.6 Febrile Neutropenia

Fever of greater than 38°C, in association with an ANC less than 500/mm^3, must prompt immediate drawing of all appropriate cultures and initiation of broad-spectrum antibiotics. Failure of febrile episodes to resolve on antibiotics should prompt consideration for institution of a broad-spectrum antifungal therapy.

7.7 Nutritional Support

All patients will most likely require total parenteral nutrition (TPN) during consolidation. This should be initiated as soon as the patient's oral intake declines and usually concomitant with initiation of the cytoreductive chemotherapy and no later than day +1 following AuHPCR. As soon as the oropharyngeal mucositis resolves, TPN should be tapered and discontinued as rapidly as is metabolically feasible, and

oral intake should be encouraged. Any subsequent need for hyperalimentation in the post-AuHPCR period is optimally achieved *via* the enteral route, either with nasogastric or gastrostomy feeds rather than with TPN, since the latter is associated with a higher risk of catheter-related infections and with the development of subsequent hepatic dysfunction.

7.8 Nephrotoxic Drugs

Patients being treated on this protocol will receive nephrotoxic chemotherapeutic agents and may develop compromised renal function. Therefore, it is important to bear in mind that aminoglycoside antibiotics, amphotericin B and certain other antibiotics are inherently nephrotoxic. Careful monitoring of renal function, by noting serum blood urea nitrogen (BUN), creatinine, electrolytes, and creatinine clearance should be undertaken when using these agents. Abnormal renal function requires modifications of antibiotic doses and dose intervals, which can be most rationally determined by monitoring peak and trough antibiotic levels in the blood.

7.9 Corticosteroid Use

Patients requiring ongoing corticosteroids (not at replacement doses), usually dexamethasone, because of mass effect and edema from residual tumor, must be weaned off of corticosteroids prior to initiation of Consolidation Phase chemotherapy. Corticosteroids not only render patients more susceptible to sepsis but can also mask the early signs of symptoms of sepsis. It is particularly important to be vigilant in monitoring such patients for the slightest suggestion of developing infection. These patients should have daily surveillance blood cultures drawn during the period of neutropenia. Corticosteroids at replacement doses will be allowed during the consolidation phase. Patients who have recently discontinued corticosteroids should be administered stress dose corticosteroids if/when readmitted with febrile neutropenia.

8.0 DRUG INFORMATION

8.1 Carboplatin (Paraplatin®, Cis-diamine (1,1-cyclobutane-dicarboxylato)-platinum)
NSC #241240

8.1.1 Description and Mechanism of Action:

The mechanism of action of carboplatin would appear to be similar to that of cisplatin. It binds to replicating DNA causing single strand breaks and interstrand cross-links with DNA. Data suggests that other factors also contribute to cytotoxicity. The α t½ is 1.1 to 2 hours and the β t½ is 2.6 to 5.9 hours. Carboplatin is not protein bound. The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. In patients with creatinine clearances below 60 mL/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. Carboplatin dosages will require adjustment dependent on the glomerular filtration rate.

8.1.2 Drug storage, stability and reconstitution:

Carboplatin is available in 50 mg, 150 mg, 450 mg and 600 mg vials.

Aqueous Solution: Carboplatin aqueous solution is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin in multidose vials. Unopened vials of carboplatin aqueous solution are stable to the date indicated on the package when stored at 25° C (77° F); excursions permitted from 15°-30° C (59°-86° F). Protect from light. Carboplatin aqueous solution multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25º C following multiple needle entries.

Powder for Injection: Carboplatin powder for injection is a sterile lyophilized white powder in single dose vials containing equal parts by weight of carboplatin and mannitol. Unopened vials of carboplatin are stable to the date indicated on the package when stored at 15°-30° C (59°-86° F). Protect from light.

Reconstitute lyophilized powder to concentration of 10 mg/ml with sterile water for injection, 5% Dextrose, Normal Saline or use premixed 10mg/ml aqueous solution. May further dilute in dextrose or saline containing solutions to a final concentration as low as 0.5 mg/ml and infuse over 60 minutes. Carboplatin solutions, when prepared as directed are stable for 8 hours at room temperature. May use institutional and clean room standards for stability. Aluminum can react with carboplatin, causing precipitate formation and potency loss. Do not use needles or IV administration sets containing aluminum parts that may come in contact with carboplatin for the preparation or administration of the drug.

8.1.3 Supplier: Commercially available from various manufacturers. See package insert for more detailed information.

8.1.4 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Hypersensitivity[2] reactions (anaphylaxis, bronchospasm, hypotension), constipation, diarrhea	Metallic taste, rash, mucositis
Prompt: Within 2-3 weeks	Myelosuppression[1] (anemia, neutropenia, leucopenia, thrombocytopenia) Electrolyte abnormalities (↓ Na, K Ca Mg)	↑LFTs (alkaline phosphatase, AST/SGOT, bilirubin), abdominal pain, nephrotoxicity (↓GFR, ↑ Cr and Bun)	
Delayed: Any time later during therapy, excluding the above conditions		ototoxicity (ringing in the ears and hearing loss)	Alopecia, temporary loss of vision to light and colors, peripheral neuropathy (with mild parethesias, diminished sense of vibration, light touch, pinprick and joint position)
Late: Any time after completion of treatment			Secondary leukemia

1 Thrombocytopenia is more severe and can be dose limiting.
2 Hypersensitivity reactions are seen more frequently with repeated courses of therapy (after 6 cycles in adults).

8.2 Etoposide (VePesid®, Etopophos®,VP-16) NSC #141540

8.2.1 Description and Mechanism of Action:

A semisynthetic derivative of podophyllotoxin that forms a complex with topoisomerase II and DNA which results in single and double strand DNA breaks. Its main effect appears to be in the S and G2 phase of the cell cycle. The initial t½ is 1.5 hours and the mean terminal half-life is 4 to 11 hours. It is primarily excreted in the urine. In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours.

The mean renal clearance of etoposide is 7 to 10 mL/min/m² or about 35% of the total body clearance over a dose range of 80 to 600 mg/m². Etoposide, therefore, is cleared by both renal and non-renal processes, i.e., metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known. Biliary excretion appears to be a minor route of etoposide elimination. Metabolism accounts for most of the non-renal clearance of etoposide.

Etoposide phosphate is a water-soluble ester of etoposide, which is rapidly and completely converted to etoposide in plasma. Pharmacokinetic and pharmacodynamic data indicate that etoposide phosphate is bioequivalent to etoposide when it is administered in molar equivalent doses.

The maximum plasma concentration and area under the concentration time curve (AUC) exhibit a high degree of patient variability. Etoposide is highly bound to plasma proteins (~94%), primarily serum albumin. Pharmacodynamic studies have shown that etoposide systemic exposure is related to toxicity. Preliminary data suggests that systemic exposure for unbound etoposide correlates better than total (bound and unbound) etoposide. There is poor diffusion into the CSF < 5%.

8.2.2 Drug storage, stability and reconstitution:

Etoposide for injection is available in sterile multiple dose vials. The pH of the clear, nearly colorless to yellow liquid is 3 to 4. Each mL contains 20 mg etoposide, 2 mg citric acid, 30mg benzyl alcohol, 80 mg modified polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. Vial headspace contains nitrogen. Unopened vials of Etoposide are stable until expiration date on package at room temperature (25°C). Etoposide phosphate for injection is available for intravenous infusion as a sterile lyophilized powder in single-dose vials containing etoposide phosphate equivalent to 100 mg etoposide, 32.7 mg sodium citrate USP, and 300 mg dextran 40. Etoposide phosphate must be stored under refrigeration 2°-8°C (36°- 46°F). Unopened vials of etoposide phosphate are stable until the expiration date on the package.

Reconstitute with NS or D5W to achieve a final concentration of 0.2 - 0.4 mg/ml. If solutions are prepared with concentrations above 0.4-mg/ml precipitations may occur.

Stability is based on dilution. Vials diluted with NS or D5W as recommended (concentration of 0.2 and 0.4 mg/ml) are stable for 48 hours. Discard if precipitate is noted.

8.2.3 Supplier:

Commercially available. See package insert for more detailed information.

8.2.4 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Anorexia, hypotension during infusion	Transient hypotension during infusion; anaphylaxis (chills, fever, tachycardia, dyspnea, bronchospasm, hypotension)
Prompt: Within 2-3 weeks	Myelosuppression (anemia, leukopenia), alopecia	Thrombocytopenia, diarrhea, abdominal pain, asthenia, malaise, rashes and urticaria	Peripheral neuropathy, mucositis, hepatotoxicity, chest pain, thrombophlebitis, congestive heart failure, Stevens-Johnson Syndrome, exfoliative dermatitis
Delayed: Any time later during therapy, excluding the above conditions			Dystonia, ovarian failure, amenorrhea, anovulatory cycles, hypomenorrhea, onycholysis of nails
Late: Any time after completion of treatment			Secondary malignancy (preleukemic or leukemic syndromes)
Unknown frequency and timing	Fetal toxicities and teratogenic effects of etoposide have been noted in animals.		

8.3 **Gemcitabine** (Gemzar®, NSC# 613327)

8.3.1 Description and Mechanism of Action:

Gemcitabine (2'-deoxy-2',2'-difluorocytidine monohydrochloride), an analog of cytosine arabinoside (Ara-C) is a novel pyrimidine anti-metabolite. The mechanism of action of gemcitabine has been well characterized. It can be deaminated to difluorodeoxycytidine deaminase or converted to dFdCMP by deoxycytidine kinase. Difluorodeoxyuridine is inactive, while dFdCMP is further metabolized to dFdCDP and dFdCTP, which, when incorporated into DNA, results in chain termination. In comparison to Ara-C incorporation into DNA, dFdCTP is less readily excised from DNA by DNA exonuclease. Thus, dFdCTP accumulates intracellularly to a greater degree than Ara-C. This may account, in part, for its different spectrum of preclinical and clinical activities. In addition, gemcitabine inhibits ribonucleotide reductase, an enzyme that produces deoxynucleotides that are required for DNA synthesis. Gemcitabine activity has been demonstrated in breast, ovarian, bladder, esophageal, and lung carcinoma.

8.3.2 Drug storage, stability and reconstitution:

Gemcitabine is supplied as a lyophilized powder in sterile vials containing 200mg or 1.0gm of gemcitabine as the hydrochloride salt (expressed as the free base), mannitol, and sodium acetate. The lyophilized product should be stored below 30 degree C. No degradation of the drug product in the dry state (vials) has been observed after six months at 40 degrees C with 75% relative humidity or after three years at room temperature.

To reconstitute, add 5ml of 0.9% sodium chloride to the 200mg vial or 25ml of 0.9% sodium chloride to the 1.0gram vial. These dilutions each yield a gemcitabine concentration of 38 mg/ml. An appropriate amount of drug will be prepared with normal saline and administered as a continuous infusion for 30 minutes. Once the drug has been reconstituted, it should be stored at room temperature and used within 24 hours. Do not refrigerate solutions of reconstituted gemcitabine as crystallization may occur. Store at room temperature 20-25 degree C (68-77 degrees F).

Normal saline is the only diluent approved for intravenous administration. Do not use other diluents. It should be noted that the pH of the undiluted solution is around 3. There may be some local irritation due to the low pH (pain at the injection site). Gemcitabine is not a vesicant; extravasation should be handled according to local hospital policy concerning extravasation of drugs.

Supplier: Commercially available. See package insert for more detailed information.

8.3.4 Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, phlebitis, edema, flu-like symptoms, rash (L), mild diarrhea or constipation	Somnolence (L), dyspnea	Hypotension, hemolytic uremic syndrome
Prompt: Within 2-3 weeks	Myelosuppression, liver function abnormalities, proteinuria, hematuria	Mucositis, weakness (L)	Renal dysfunction, confusion, seizure (L), coma (L), pulmonary edema-noncardiogenic, possibly fatal
Delayed: Any time later during therapy, excluding the above conditions		Alopecia, paresthesias, itching	
Late: Any time after completion of treatment			

(L) Toxicity may also occur later

8.4 Granulocyte Colony Stimulating Growth Factor (r-metHuG-CSF, G-CSF, Filgrastim, Neupogen®) NSC #614629

8.4.1 Description and Mechanism of Action:

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons manufactured by recombinant DNA technology utilizing E coli bacteria into which has been inserted the human granulocyte colony stimulating factor gene. It differs from the natural protein in that the N- amino acid is methionine and the protein is not glycosylated.

G-CSF is a lineage specific colony-stimulating factor, which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).

The elimination half-life is similar for subcutaneous and intravenous administration, approximately 3.5 hours. The time to peak concentration when administered subcutaneously is 2 to 8 hours.

8.4.2 Drug Storage, Stability and Reconstitution:

Supplied as a clear solution in 300 mcg/ml 1 ml or 1.6 ml vials and prefilled syringes containing 300 mcg/0.5mL or 480 mcg/0.8mL. Vials are preservative free single use vials. Discard unused portions of open vials. Store refrigerated at 2-8º C (36-46ºF). Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Avoid freezing and temperatures > 30ºC.

For IV use, dilute in D5W **only** to concentrations >15 mcg/ml. At concentrations between *5* and 15 mcg/ml, human serum albumin should be added to make a final albumin concentration of 0.2% (2 mg/ml) in order to minimize the adsorption of filgrastim to infusion containers and equipment. Dilutions of 5 mcg/ml or less are not recommended. Diluted filgrastim should be stored at 2-8º C (36-46ºF) and used within 24 hours. **Do not shake.**

8.4.3 Supplier: Commercially available from various manufacturers. See package insert for further information.

8.4.4 Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Local irritation at the injection site, headache	Allergic reactions
Prompt: Within 2-3 weeks	Mild to moderate medullary bone pain,	Increased alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, exacerbation of pre-existing skin rashes, sickle cell crises in patients with SCD, excessive leukocytosis
Delayed: Any time later during therapy, excluding the above conditions			Cutaneous vasculitis, ARDS
Late: Any time after completion of treatment			

8.5 **Oxaliplatin** (Eloxatin®, SR9669) NSC # 266046, IND # 57004

8.5.1 Description and Mechanism of Action:

Oxaliplatin is a third generation platinum agent characterized by a DACH (1,2 diaminocyclohexane) ligand. Once infused, oxaliplatin undergoes biotransformation into active metabolites. The oxalate ligand in the parent compound is replaced by either Cl- or HCO3 - ions to yield dichloro-DACH platin, monochloro-DACH platin, and diaquo-DACH platin. Studies on the mechanism of action of oxaliplatin, although not completely elucidated, show that the aqua-derivatives resulting from the biotransformation of oxaliplatin interact with DNA to form both inter- and intra-strand cross links, resulting in the disruption of DNA synthesis leading to cytotoxic and antitumor effects. Oxaliplatin does not undergo cytochrome-P450 metabolism in the liver. Renal clearance accounts for approximately 50% of total oxaliplatin clearance. Pharmacokinetic data in children is pending. In adults the approximate half-lives are: t½α = 0.28 hrs, t½β = 16.3 hrs, t½γ = 273 hrs.

8.5.2 Drug storage, stability and reconstitution:

Supplied as freeze-dried powder for intravenous infusion in vials containing 50 mg or 100 mg of oxaliplatin. The powder is a white to off-white cake or powder contained in clear glass vials, sealed with an elastomeric stopper and aluminum seal with a flip-off cover. The excipient is lactose monohydrate, 450mg and 900mg, respectively. Store the intact vials at controlled room temperature (150 - 300 C, not to exceed 300 C).

The freeze-dried powder is stable for 3 years at room temperature and protected from light in the original cartons. The freeze-dried powder is reconstituted by adding 10 mL (for the 50 mg vials) or 20 mL (for the 100 mg vials) of Water for Injection or Dextrose 5% in Water to yield a 5 mg/mL solution. This mixture in the original vial is stable for 48 hours under refrigeration (2-8ºC). For administration, the 5 mg/mL reconstituted solution must be further diluted with Dextrose 5% in water to a final volume between 250 mL to 500 mL. This preparation is stable for 24 hours under refrigeration (2-8ºC) or for 6 hours at room temperature (20-25ºC). Oxaliplatin concentration of the final dilution should not be less than 0.2 mg/mL. For smaller patients in whom volume may be of concern, a final concentration of 0.3-to 0.6 mg/ml oxaliplatin is acceptable. However, the dose needs to be mixed immediately prior to administration to ensure stability of oxaliplatin at this concentration range. Once the appropriate dose of oxaliplatin is calculated, the drug will be diluted with Dextrose 5% in water to a total volume between 250 mL to 500 mL. The infusion should be administered over 2 hours.

Oxaliplatin should never be reconstituted or diluted with a sodium chloride solution. Never use aluminum-containing needles or intravenous infusion sets to prepare or administer oxaliplatin. Never mix oxaliplatin with alkaline drugs, as it is unstable in alkaline conditions.

8.5.3 Supplier: Commercially available. See package insert for more detailed information.

8.5.4 Toxicity :

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Headache, rhinitis, dyspepsia, taste perversion, dizziness, hand-foot syndrome, flushing, rash, insomnia, anorexia, hypersensitivity, rigors, hematuria, dysuria, phlebitis	Hiccup, flatulence, dysphasia, dyspnea, cough, dehydration, tachycardia, drug fever, ataxia, pharyngolaryngeal dysesthesia with subjective sensations of dysphagia or dyspnea with/without laryngospasm or bronchospasm, extravasation (rare), anaphylaxis, hypertension, chest pain
Prompt: Within 2-3 weeks, prior to the next course		Nose bleed, weight loss, mucositis/stomatitis, esophagitis, alopecia, peripheral edema, arthralgia, upper respiratory infection, pharyngitis, elevated serum creatinine, hypokalemia	Fatigue, neutropenia, thrombocytopenia, anemia, infection, transient increase in liver function tests, thromboembolism, DIC, visual abnormalities exacerbated by cold temperatures, elevated AST, ALT, Alkaline phosphatase, bilirubin, noninfectious otitis, enteritis, ileus and GI obstruction, hypocalcemia, hypomagnesemia, hyponatremia, elevated uric acid and acidosis, depression, bone pain, urinary retention, ocular surface disease, extrapyramidal movements, pancreatitis
Delayed: Any time later during therapy, excluding the above conditions	Persistent paresthesias of mouth/throat and extremities (may be exacerbated by cold temperatures)		Pulmonary fibrosis, venooclusive disease in combination regimens (hepatomegaly, splenomegaly, portal hypertension, esophageal varices), renal failure, ototoxicity

(L) Toxicity may also occur later.

8.6 Paclitaxel (Taxol®, NSC # 125973)

8.6.1 Description and Mechanism of Action:

Paclitaxel is a diterpene plant product derived via a semi-synthetic process from the bark of the Western Yew, *Taxus brevifolia*. Paclitaxel is an anti-microtubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Paclitaxel is metabolized via the cytochrome P450 isoenzyme CYP2C8 to one major metabolite (6-alpha-hydroxypaclitaxel), and via the cytochrome P450 isoenzyme CYP3A4 to two minor metabolites (3-para-hydroxypaclitaxel and 6-alpha, 3"-para-dihydroxypaclitaxel). The terminal half-life ranged from 5.3 to 17.4 hours, following 1-hour and 6-hour infusions at doses of 15 to 275 mg per square meter of body surface area. The elimination of paclitaxel is not completely understood. The mean values for urinary recovery of unchanged drug following 1-, 6-, and 24-hour infusions at doses of 15 to 275 mg per square meter of body surface area ranged from 1.3% to 12.6% of the dose, indicating extensive nonrenal clearance. High concentrations of paclitaxel and its metabolites have been reported in the bile and recovery of paclitaxel in the feces accounted for 5% of an administered dose. Total recovery of paclitaxel and metabolites in the feces accounted for 56% to 101% of an administered dose. *In vitro* studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicate that between 89%-98% of drug is protein bound. Dosage reduction may be required in hepatic dysfunction. Caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4.

8.6.2 Drug storage, stability and reconstitution:

Paclitaxel is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP. Unopened vials of paclitaxel injection are stable until the date indicated on the package when stored between 20°-25° C (68°-77°F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration components in the paclitaxel vial may precipitate, but redisolves upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded.

Dilute in dextrose or saline solutions to a final concentration between 0.3-1.2 mg/ml (use standard dilution volumes of 50, 100, 250, 500, 1000 ml) and infuse over 3 hours using non-PVC containers and administration equipment. An inline 0.22 micron filter should be used during administration. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C) and room lighting conditions.

Premedicate patients with a corticosteroid, diphenhydramine, and an H2-receptor antagonist 30 minutes prior to paclitaxel administration. The paclitaxel is given over a 3-hour infusion. The paclitaxel is diluted to a concentration of 1.0 mg/ml in D5W, and should incorporate in-line filtration. The rate of infusion over the first 30 minutes will be 25% of the overall infusion rate.

8.6.3 Supplier: Commercially available from various sources. See package insert for more detailed information.

8.6.4 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Abnormal ECG, asthenia, myalgia, arthralgia, nausea, flushing, anorexia	Diarrhea, vomiting, dyspnea, peripheral edema, cough, rash, hypotension	Anaphylaxis with dyspnea, hypotension, flushing, chest pain, and tachycardia, angioedema, urticaria, hypertension, chills, back pain, venous thrombosis, chest pain, arrhythmias (bradycardia, V tach, bigeminy, SVT, atrial fib, AV block), MI, injection site reaction (erythema, tenderness, skin discoloration, or swelling at the injection site, rarely: phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis) (L)
Prompt: Within 2-3 weeks	Alopecia, neutropenia, anemia, sensory neuropathy, elevated SGOT (AST), alkaline phosphatase, mucositis	Infections, elevated bilirubin, thrombocytopenia	Febrile neutropenia, hemorrhage, grand mal seizures, syncope, ataxia, neuroencephalopathy, paralytic ileus, maculopapular rash, pruritis, Stevens-Johnson syndrome, toxic epidermal necrolysis, conjunctivitis and increased lacrimation
Delayed: Any time later during therapy, excluding the above conditions			CHF, interstitial pneumonia, lung fibrosis, pulmonary embolism, optic nerve and/or visual disturbances, ototoxicity (hearing loss and tinnitus), hepatic necrosis, hepatic encephalopathy, nail changes (changes in pigmentation or discoloration of nail bed)

Late: Any time after completion of treatment			

(L) Toxicity may also occur later

8.7 Thiotepa (Tespa, Thiophosphamide, Triethylenethiophosphoramide Tspa, WR-45312)

8.7.1 Description and Mechanism of Action:

Thiotepa is a cytotoxic agent of the polyfunctional type, related chemically and pharmacologically to nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethylenimine radicals, which, like irradiation, disrupt the bonds of DNA. One of the principal bond disruptions is initiated by alkylation of guanine at the N-7 position, which severs the linkage between the purine base and the sugar and liberates alkylated guanines. Thiotepa is desulfurated by cytochrome P-450 enzymes such as 2B1 and 2C11, which catalyze the conversion of thiotepa to tepa. Tepa is less toxic than thiotepa and has been demonstrated to produce alkali-labile sites in DNA, rather than cross-links. These findings indicate that tepa reacts differently from thiotepa and produces monofunctional alkylation of DNA. A second metabolite of thiotepa, a mercapturic acid conjugate, is formed via glutathione conjugation. Monochloro tepa is the third metabolite found in the urine. Following short intravenous infusion (less than 5 minutes), peak concentrations of thiotepa were measured within 5 minutes. At steady state, the volume of distribution was independent of dose and ranged from 0.3 to 1.6 liters per kilogram (l/kg). Approximately 4.2% of the original dose is eliminated in the urine within 24 hours as tepa. The elimination half-life of thiotepa ranges from 2.3 to 2.4 hours. The half-life of tepa ranged from 3.0 to 21.1 hours in one study.

8.7.2 Drug storage, stability and reconstitution:

Thiotepa for Injection USP, for single use only, is available in vials containing 15 mg of nonpyrogenic, sterile lyophilized powder. Store in a refrigerator at 2° to 8°C (36° to 46°F). **PROTECT FROM LIGHT AT ALL TIMES.**

Guidelines for Administration: Reconstitute thiotepa for injection with 1.5 mL of Sterile Water for Injection resulting in a drug concentration of approximately 10 mg/mL**.** (As per manufacturer's information: Actual content per vial 15.6mg; withdrawable amount 14.7mg/1.4ml; approximate reconstituted concentration: 10.4mg/ml). When reconstituted with Sterile Water for Injection, solutions of thiotepa should be stored at refrigerated temperatures 2° to 8°C (36° to 46°F) and used within 8 hours. The reconstituted solution is hypotonic and should be further diluted with Sodium Chloride Injection (0.9% NaCl) prior to use. Reconstituted solutions further diluted with Sodium Chloride Injection should be used immediately. In order to eliminate haze, filter solutions through a 0.22 micron filter [Polysulfone membrane (Gelman's Sterile Aerodisc®, Single Use) or triton-free mixed ester of cellulose/PVC (Millipore's MILLEX®- GSFilter Unit)] prior to administration. Filtering does not alter solution potency. Reconstituted solutions should be clear. Solutions that remain opaque or precipitate after filtration should not be used. When thiotepa is given in bone marrow transplant doses, bathe the patient frequently (≥ 2 baths/day) to avoid the contact dermatitis and discoloration of the skin that is seen with high dose.

8.7.3 Supplier: Commercially available from various manufacturers. See package insert for further information.

8.7.4 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, anorexia, fatigue, Weakness	Pain at the injection site, Dizziness, headache, blurred vision, abdominal pain, Contact dermatitis, rash	Anaphylaxis, laryngeal edema, wheezing, hives
Prompt: Within 2-3 weeks	Myelosuppression; At higher doses in conditioning regimens for BMT: mucositis, esophagitis	At higher doses in Conditioning regimens for BMT: inappropriate behavior, confusion, somnolence, increased liver transaminases, increased bilirubin, hyperpigmentation of the skin	Febrile reaction, Conjunctivitis, dysuria, urinary retention
Delayed: Any time later during therapy, excluding the above conditions	gonadal dysfunction/infertility, azoospermia, amenorrhea		Alopecia, Secondary Malignancy
Unknown Frequency and Timing:	Fetal and teratogenic toxicities: Carcinogenic and teratogenic effects of thiotepa have been noted in animal models at doses ≤ to those used in humans. It is not known if thiotepa is excreted into human breast milk.		

(L) Toxicity may also occur later

9.0 REQUIRED OBSERVATIONS

9.1 Required Observations Before and During Protocol Therapy

Studies	Baseline	Prior to each cycle of induction	End of induction	Prior to second look surgery	Following second look surgery	Prior to starting consolidation	During consolidation	End of therapy** (Day +42)
Height, weight and BSA	X	X	X	X	X	X	X	X
Cranial MRI with and without gadolinium	X[2]		X[4]	X	X[2]	X		X
Spine MRI with and without gadolinium	X[3]		X[4]	X	X[3]	X		X
Lumbar CSF cytology and tumor markers (AFP and HCGβ) and MiRNA[10]	X		X[4]		X	X		X
Serum tumor markers[9](AFP and HCGβ	X	X[1]	X[4]	X	X	X		X
Serum creatinine, BUN, Calcium, Phosphate, Magnésium, Potassium, Sodium, Glucose	X	X	X	X		X	X[5]	X
AST, ALT, Total bilirubin	X	X	X			X	X[5]	X
Other Labs[8]						X		
CBC, differential, platelet count	X	X[1]	X	X		X	X[5]	X
Creatinine clearance or nuclear GFR scan						X	X[6]	
Endocrine evaluation[7]	X				X			X
Ophthalmology evaluation	X							
Pregnancy test (if applicable)	X							
Audiometry	X					X		X
Central Pathology review (for details see section 14.8.1 and 14.9)	X				X			

1= Obtain weekly.

2= All brain post-operative imaging should be done within 72 hours of surgery. If imaging cannot be obtained at this time, then it should be done after 10 days but within 21 days following surgery.

3= Either performed pre-operatively or at least 10 days after surgery and preferably performed in two planes.

4= Obtain after second and fourth induction course

5= Obtain twice weekly until engraftment.

6= Obtain prior to each dose of carboplatin to calculate the Calvert formula.

7= Endocrine evaluations for each patient in therapy consist of free T4, TSH, IGF1, IGFBP3, LH (in males, over age10, or in females, over age 9), FSH (in males, over age 10, or in females over age 9), Testosterone (in males over age 10), estradiol (in females, over age 9), Tanner stage, cortisol 8AM, Na, K, Cl, CO2, BUN, Cr, first morning void specific gravity. If any endocrine parameter is abnormal, then referral to a pediatric endocrinologist for further evaluation, dynamic testing, and treatment is required.

8= Antibody titers to: cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus (VZV), human immunodeficiency virus (HIV), hepatitis A, B and C viruses. Also, hepatitis B surface antigen should be tested.

9= Serum markers should be obtained around the same time when CSF markers are obtained. If serum markers are obtained prior to CSF analysis, then serum markers should be repeated at the time of CSF marker analysis.

10= MiRNA optional research study

**= If Radiation therapy is given following consolidation then end of therapy will be calculated from the completion of the radiation therapy.

9.2 Required Observations Following Completion of Protocol Therapy

Studies	3 months	6 months	9 months	12 months	16 months	20 months	24 months	30 months	36 months	Annually after 3 years
Height, weight	X	X	X	X	X	X	X	X	X	X
Cranial MRI with and without gadolinium	X	X	X	X	X	X	X	X	X	X
Spine MRI with and without gadolinium[3]	X	X	X	X	X	X	X	X	X	X
Serum tumor markers and MiRNA	X	X	X	X	X	X	X	X	X	X
Serum creatinine, BUN, Ca, Magnésium, Potassium, Sodium	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
AST, ALT, Total bilirubin	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X X[1]
CBC, differential, platelet count	X	X	X	X	X	X	X	X	X	X
Endocrine evaluation[2]		X		X			X		X	X

1= Repeat if abnormal on a monthly basis until stable or normalized after the end of therapy. If normal at the end of therapy then repeat only as clinically indicated.

2= Endocrine evaluations for each patient in therapy consist of free T4, TSH, IGF1, IGFBP3, LH (in males, over age 10, or in females, over age 9), FSH (in males, over age 10, or in females over age 9), Testosterone (in males over age 10), estradiol (in females, over age 9), Tanner stage, cortisol 8AM, Na, K, Cl, CO2, BUN, Cr, first morning void specific gravity. If any endocrine parameter is abnormal, then referral to a pediatric endocrinologist for further evaluation, dynamic testing, and treatment is required.

3= If the on-study evaluation is negative, then MRI spine do not need to be repeated thereafter, unless the patient demonstrates radiographic or tumor marker evidence of disease recurrence or progression.

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Progressive disease.
b) Failure to fulfill criteria to proceed to Consolidation (see Section 5.3).
c) Refusal of further protocol therapy by patient/parent/guardian.
d) Completion of protocol therapy.
e) Physician determines it is in patient's best interest.
f) Grade 4 paclitaxel hypersensitivity toxicity.

Patients who are off protocol therapy are to be followed until they meet the criteria for off study (see below). Follow-up data will be required unless consent was withdrawn.

10.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Entry into another therapeutic study.
d) Withdrawal of consent for any further data submission.
e) Tenth anniversary of study closure to accrual.

11.0 STAGING AND EVALUATION CRITERIA

11.1 Staging and Pre-Treatment Evaluation

11.1.1 Definitions of M (Metastatic) Strata

There are 3 staging stratum: M+, modified M+ and M0.

1. M+ (disseminated disease):
   - Leptomeningeal or intraventricular metastases visualized on MRI scans of the brain and spine.
   - Clumps of tumor cells on lumbar CSF cytology.
   - Visible tumor studding the walls of the lateral or third ventricles noted during endoscopy or surgery.
   - Primary tumor arising within the parenchyma of the brain, brainstem or spinal cord.
   - Measurable multi-focal tumors arising in both the pineal and suprasellar regions (multiple midline tumors).
   - Infiltrative, intra-axial extension on brain MRI > 1 cm beyond enhancing tumor.

2. Modified M+ (occult multi-focal disease):
   - M0 at diagnosis with a localized pineal region tumor with signs and symptoms of diabetes insipidus without measurable disease in the suprasellar region.
   - M0 at diagnosis (either pineal or suprasellar primary), and there is ≥ 65 % volumetric or ≥ 50% area reduction from baseline of the presumed uninvolved suprasellar or pineal region site on MRI after the completion of chemotherapy (see Section 11.3).

3. M0 (localized disease):

   - None of the above.

11.1.2 Definition of the Primary Tumor Site

Four categories of primary site are recognized:
- Pineal region
- Suprasellar region
- Both pineal and suprasellar regions
- Other

It may be difficult to determine the primary site in some patients who present with widespread metastases. The suggestible upper normal limit of size for the pineal gland is a maximum diameter of 10 mm in one dimension and up to 8 mm in the remaining dimensions with a total volume less than 140 mm^3. The maximal diameter of the infundibulum is 2-3 mm in any single plane.

11.1.3 Assessment of Tumor Markers

The serum markers may be obtained prior to surgery but should be repeated at the time of CSF analysis. Lumbar ± ventricular CSF tumor markers may be obtained at the time of surgery or 1-2 weeks after surgery. Results of the CSF markers may take 5-7 days.

11.1.4 Other Staging Considerations

- Parts of the staging evaluation can be performed before or within 2 weeks following surgery. The brain and spine enhanced MRI may be obtained prior to surgery. If the spine MRI is performed prior to surgery, than only the brain MRI need be repeated post-op. This should be performed within 72 hours of surgery. It is desirable to perform the lumbar puncture either during surgery or within the first or second week following surgery, assuming any raised intracranial pressure has been controlled with a third ventriculostomy or ventriculo-peritoneal shunt.
- Although radical resection of the primary CNS germ cell tumor is not recommended, the patient is still eligible for this protocol if the tumor is totally resected and there is no other evaluable disease.
- Although this study is eager to accumulate CSF data from ventricular fluid obtained at the time of surgery, only the results of a lumbar CSF analysis will be used for the determination of protocol eligibility and staging. There may be the unusual circumstance when the neurosurgeon advises against a post-op lumbar puncture.

11.2 Methodology to Determine Tumor Measurement

11.2.1 Response Determination using 3-D Measurements

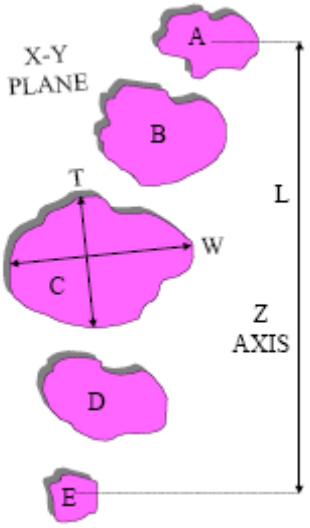
Three rather than 2-dimensional tumor measurements are preferred for all target lesions. Tumor response criteria are determined by changes in all 3 dimensional measurements: width (W), transverse (T), and length (L) measurements.

Reports for the follow-up exams should reiterate the measurements obtained at baseline for each target lesion. Non-target lesions or newly occurring lesions should also be enumerated in these reports and changes in non-target lesions should be described.

3-D measurements can be made using either T1 or T2 weighted images (which ever gives the best estimate of tumor size). The longest diameter (W) can be measured in the imaging plane (i.e. axial, coronal or sagittal) in which the tumor is best measured, provided the same plane is used in follow up studies. The transverse (T) measurement is perpendicular to the width in the selected plane, and the entire length (L) is the tumor extent in the plane perpendicular to the selected plane. This latter measurement may be easily calculated on the MRI scan by summing the slice position (SP) or table position (TP) of all the images in which the tumor is visible and then adding one additional gap thickness. (See drawing below for illustration).

GUIDELINES: TUMOR SIZE MEASUREMENT BASED ON CROSS-SECTIONAL IMAGING

- A, B, C, D, & E are contiguous parallel slices in the X-Y plane (usually axial) showing the tumor
- W and T are the maximal perpendicular diameters on the slice (C in this example) showing the largest surface area.
- Tumor length in the Z-axis (L) (perpendicular to X-Y plane) can be obtained either by the [a] (difference in table position of the first and last slices showing the tumor + one slice thickness), or [b] the product of (slice thickness + gap) and the number of slices showing the tumor.



Only the solid component of cystic/necrotic tumor should be measured. If cysts/necrosis composes the majority of the lesion, the lesion may not be "measurable".
Leptomeningeal tumor spread is not a target lesion and cannot be measured in a quantitative fashion.

Presence and location of leptomeningeal tumor spread should be noted as well as changes in extent/thickness assessed on follow up studies.

11.2.2 Overall Response Assessment

The overall response assessment takes into account response in both target and non-target lesion, and the appearance of new lesions, and normalization of markers, where applicable, according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, marker, and new lesions in the preceding columns.

Target Lesions	Non-Target Lesions	New Lesions	Markers Normal/Abnormal/Rising	Overall Response
CR	CR	No	Normal	**CR**
CRU	CR or CRU	No	Normal	**CRU**
CR or CRU	CR	No	Normal	**CRU**
CR or CRU	Non-PD	No	Normal	**PR[1]**
PR	Non-PD	No	Normal	**PR[1]**
CR or PR	Non-PD	No	Abnormal – not rising	**PR[2]**
SD	Non-PD	No	Normal/Abnormal-not rising	**SD**
Any	Any	Any	Abnormal-rising	**PD**
SD	Non-PD	*Yes*	Any	**PD**
PD	Any	Any	Any	**PD**
Any	PD	Any	Any	**PD**
Any	Any	Yes	Any	**PD**

1= Partial Response with normal markers

2= Partial Response with abnormal (but not rising) markers

The sections that follow discuss the selection and evaluation of each of these types of lesions.

11.2.3 Selection of Target and Non-Target Lesions

- For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response.
- If multiple measurable lesions are present, up to 5 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions.
- The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g. 8 mm lesion for a 4 mm slice).
- Any change in size of non-target lesions should be noted, though does not need to be measured.

11.3 Response Criteria

11.3.1 Response Criteria for Target Lesions

1. Response criteria are assessed in **3 dimensions** – the product of Length (L) x W (longest perpendicular diameter) x T (transverse length). An elliptical model volume (=0.5 L x W x T) is used.

2. To assess response/progression, the ratio is calculated:

$$\frac{L \times W \times T \text{ (current scan)}}{L \times W \times T \text{ (reference scan)}}$$

3. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g. when multiple lesions show opposite responses, the progressive disease takes precedence.

11.3.2.1 Response Criteria for target lesions:

Complete Response (CR): Disappearance of all target lesions.

Complete Response with Unconfirmed Residual (CRU): Small residual lesion, unclear if scar *versus* tiny resdidual tumor, no greater than 1cm in maximal tumor diameter excluding any area of calcification.

Very Good Partial Response (VGPR): Small residual lesion, representing > 90% decrease in the sum of the products of the three perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.

Partial Response (PR): ≥65% decrease in the sum of the products of the three perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.

Stable Disease (SD): Neither sufficient decrease in the sum of the products of the three perpendicular diameters of all target lesions to qualify for PR (taking as reference the initial baseline measurements), nor sufficient increase in a single target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started).

Sufficient Response (SR): Complete response, partial response, or stable disease, without Dexamethasone dependency.

Progressive Disease (PD): 40% or more increase in the product of perpendicular diameters of ***any*** target lesion, taking as reference the smallest product observed since the start of treatment, or the appearance of one or more new lesions.

11.3.2.2 In the rare circumstance that the length of a lesion cannot be determined, then comparison of **2 dimensional measurements**, T x W (product of the longest diameter and its longest perpendicular diameter) can be used:

Complete Response (CR): Disappearance of all target lesions.

Complete Response with Unconfirmed Residual (CRU): Small residual lesion, unclear if scar versus tiny resdidual tumor, no greater than 1cm in maximal tumor diameter excluding any area of calcification.

Very Good Partial Response (VGPR): Small residual lesion, representing > 80% decrease in the sum of the products of the two perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.

Partial Response (PR): ≥50% decrease in the sum of the products of the two perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.

Stable Disease (SD): Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR (taking as reference the initial baseline measurements), nor sufficient increase in a single target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started).

Sufficient Response (SR): Complete response, partial response, or stable disease, without Dexamethasone dependency.
Progressive Disease (PD): 25% or more increase in the product of perpendicular diameters of ***any*** target lesion, taking as reference the smallest product observed since the start of treatment, or the appearance of one or more new lesions.

11.3.3 Response Criteria for Non-target Lesions

Complete Response (CR): Disappearance of all non-target lesions.

Partial Response/Stable Disease (PR/SD): The persistence of one or more non-target lesions.

Progressive Disease (PD): The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

11.3.3 Response criteria for tumor markers

Tumor markers will be classified simply as being at normal levels or at abnormal levels.

12.0 STATISTICAL CONSIDERATIONS

12.1 Design overview

This is a phase II study of GemPOx treatment followed with HDC and AuHPCR for recurrent CNS GCT. The primary objectives of the study are first to estimate the response rate (CR/CRU/VGPR/PR) of patients with MMGCT that are able to proceed to HDC and AuHPCR after up to 4 courses of induction treatment for MMGCT patients, and second to assess the toxicities of this regimen in all CNS GCT patients. The patients who proceed to HDC and AuHPCR are those who achieve complete response (CR), complete response with unconfirmed residual (CRU), very good partial response (VGPR), or stable disease (SD), and thus these will be considered a sufficient response to treatment. The primary efficacy analysis will focus on MMGCT patients, and pure germinoma patients are included primarily for evaluation of toxicity. Less than a 50% sufficient response rate among the MMGCT patients after up to 4 courses of induction treatment is regarded insufficiently efficacious to warrant further consideration for the GemPOx regimen, and a 70% sufficient response rate is the minimum response rate of clinical interest for this regimen.

The study will be performed with a two stage design. First, 15 MMGCT patients will be enrolled and treated. If 8 or more patients exhibit a sufficient response after up to 4 courses of induction treatment, then 13 additional MMGCT patients will be enrolled and treated. The treatment regimen will be considered sufficiently efficacious if 18 or more of the 28 MMGCT patients treated achieve a response after up to 4 courses of induction treatment.

12.2 Endpoints

The primary endpoint of the study is achievement of sufficient response that enables a patient to proceed to HDC and AuHPCR after up to 4 courses of induction treatment. Patients who fail to complete induction therapy due to toxicity or complications of disease are considered evaluable for response and are classified as not having achieved a sufficient response to treatment.

Secondary endpoints for the study include:

- Time to treatment failure (TTF), which is defined as the minimum of the time to failure to achieve a sufficient response at the end of the 4th course, the time to disease progression, the time to disease recurrence following achievement of a sufficient response , or the time to death from any cause, whichever is first. TTF will be used to compute the actuarial estimate of event-free survival (EFS) percent.
- Time to death from any cause, from which the actuarial estimate of overall survival (OS) percent will be computed.

12.3 Patient accrual and statistical consideration

It is expected that approximately 10 recurrent MMGCT and 2 recurrent pure germinomas will be enrolled on this study per year. If a sufficient number of responses are observed at the end of the first stage of the study, the study will meet the accrual goal of 28 MMGCT patients within approximately 3 years. Approximately 6 recurrent pure germinomas are expected to be enrolled.

The figure below shows the power to conclude that the regimen is efficacious, as well as the average number of patients that will be treated, as a function of the true sufficient response rate after up to 4 courses of induction treatment. Note that if the regimen was not effective, e.g., if it induced sufficient responses only in 50% of MMGCT patients, then there is only a 9% chance that it would be accepted, and an average of only 22 MMGCT patients would be treated with the regimen. On the other hand, if the regimen was effective, e.g., if it induced sufficient responses in 70% of MMGCT patients, then there is a 80% chance that it would be accepted, and an average of 28 MMGCT patients would be enrolled in this case. Hence, this rule is sufficiently discriminatory to reliably rule out this regimen when it has poor efficacy but will reliably accept it when it has good efficacy.

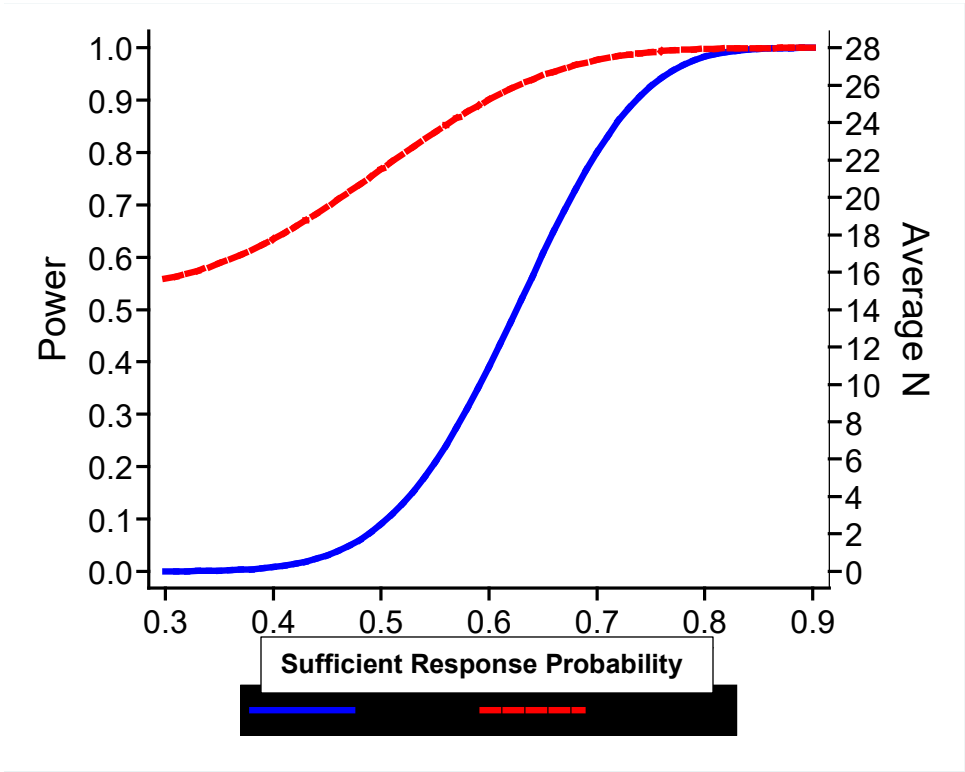


Figure: Power and Average Sample Size for Two-Stage Response Rule

12.4 Interim Monitoring of Toxic Death

The occurrence of toxic death (TD) at any time will be a primary endpoint for safety monitoring. A toxic death rate that exceeds p_0=5% will be considered unacceptable. No formal statistical rule will be employed. Rather, if the crude proportion of patients experiencing a toxic death exceeds p_0=5% at any time, the cause and circumstances of these deaths will be reviewed with the study committee and with the Data and Safety Monitoring Committee to determine whether modifications to or termination of the study is warranted. This study will be monitored by appointed Data and Safety Monitoring Board, which is a standing committee comprising expert physicians and a biostatistician at Nationwide Children's Hospital.

13.0 NEUROSURGICAL GUIDELINES

There are no "standard" neurosurgical procedures for central nervous system germ cell tumors. However, certain general guidelines, detailed below, should be considered in planning neurosurgical intervention in patients suspected of harboring such tumors.

13.1 Control of Raised Intracranial Pressure

In the majority of cases in which there is symptomatically elevated intracranial pressure (ICP), this will be secondary to obstructive hydrocephalus. It should be possible, in the short term, to control raised ICP, pending results of tumor marker (AFP and HCGβ) studies on the peripheral blood as well as head and spine MRI studies, by the administration of dexamethasone, which should be accompanied by an antacid and/or an H_2 antagonist.

However, in those patients in whom there is severely raised ICP, or in whom a delay in completing such evaluations or commencing chemotherapy is anticipated, then hydrocephalus will need to be controlled by establishment of a formal cerebrospinal fluid (CSF) diversion; in these patients, a ventriculo-peritoneal shunt or third ventriculostomy is recommended. Fears of dissemination of tumor cells to extraneural sites are largely unfounded. Additionally, the insertion of filters to "prevent" transmission of tumor cells into the abdomen is unnecessary.

At the time of shunt insertion, the opportunity should be taken to perform CSF sampling for cytology and for tumor marker studies (AFP and HCGβ) as well as CSF protein and exosomal micro RNAs (the latter performed in the laboratory of Dr. Jeffrey Leonard at NCH).

13.2 Cerebrospinal Fluid (CSF) Sampling

It is essential to obtain CSF for tumor marker studies and for cytology in this study. Clearly, the presence of an intracranial mass will raise concerns about the safety of CSF sampling in individual patients.

It is suggested that, if there are intracranial masses of less than 2 cm maximal diameter, without either symptomatic raised ICP or hydrocephalus on CAT or MRI scans, then CSF sampling by lumbar puncture is safe and appropriate. In the presence of larger intracranial masses, or symptomatic raised ICP or hydrocephalus on CAT or MRI scans, then lumbar puncture may be contraindicated and should be undertaken only after consultation between the neurosurgeon, neuro-oncologist, and neuroradiologist. In the latter circumstance, CSF could be obtained by ventricular puncture, either at the time of shunt insertion, or even at a separate procedure, if shunting is not to be performed. Such a procedure is amply justified, as the finding of positive markers in the ventricular CSF may avoid the need for an open, potentially more hazardous surgical procedure to obtain a diagnosis. Ventricular puncture could be combined with other procedures, such as insertion of an indwelling venous access catheter for chemotherapy.

13.3 Direct Tumor Surgery

13.3.1 At Diagnosis:

Study eligibility mandates pathological confirmation of germinomatous histology, in the absence of other, non-germinomatous malignant elements (e.g. yolk sac tumor, choriocarcinoma, embryonal carcinoma). Thus, all patients with no normal serum and CSF tumor makers must undergo at least a biopsy prior to study enrollment. Individual neurosurgeons may choose to consider, where appropriately indicated by tumor size and location, a radical open surgical procedure.

One scenario in which the benefits of more radical surgical resection may outweigh the risks is the patient with negative tumors markers in the serum and CSF and an enlarging mass on the brain MRI to rule out the presence of mature teratoma.

13.3.2 Second Look Surgery

In those patients with evidence of residual disease radiographically following the fourth course of protocol-specified chemotherapy, regardless of their tumor markers levels, an open surgical procedure is strongly recommended to excise the residual tumor and to determine the subsequent therapeutic plan. Such residual radiographic "tumor" may represent non-viable fibrotic tissue, mature teratoma, immature teratoma, malignant germ cell tumor, or some mixture of each.

In those patients with evidence of increasing tumor size radiographically following either second or fourth protocol-specified induction chemotherapy cycle and in whom tumor markers are normal at such time, then a surgical procedure is mandated to excise the tumor or obtain a biopsy in order to rule out " Growing Teratoma Syndrome." Patient's disease response should be deemed as progressive disease only after "Growing Teratoma Syndrome" has been ruled out. Should the patient indeed have growing teratoma syndrome, patient must continue receiving protocol therapy.

13.4 Extent of Surgical Resection

Classification of overall extent of resection for this study shall be based upon the volume of residual tumor after the final attempt at tumor resection.

13.4.1 Biopsy only:

After an open surgical or closed (stereotactic) removal of tissue for the sole purpose of establishing a pathological diagnosis, if tumor removal is less than 10% of the total tumor mass, this will be considered a biopsy only.

13.4.2 Partial Resection:

Partial resection is defined as removal of greater than 10% but less than 50% of the tumor mass. A partial resection is at all times considered to be an incomplete resection for the purpose of this study.

13.4.3 Subtotal Resection:

Removal of greater than 50% but less than or equal to 90% of the tumor mass, or greater than 1.5 cm maximal diameter residual tumor mass by post-operative radiological studies.

13.4.4 Near Total Resection:

Removal of greater than 90% but less than 100% of the tumor mass and less than 1.5 cm maximal diameter of the residual tumor mass.

13.4.5 Gross Total Resection:

No visible tumor is left following surgery, and this is confirmed by post-operative gadolinium enhanced MRI scan. It is recommended that cavity (tumor bed) biopsies be obtained following radical surgical resection, to affirm gross total resection status.

13.5 Neurosurgical On-Study Requirements

13.5.1 Completion of protocol-specific Neurosurgical Tumor Resection Form and Upload institutional operative report to REDCap, electronic data capture system. This should be undertaken separately for each neurosurgical procedure.

13.5.2 Submission of the operating neurosurgeon's institutional operative report for each separate neurosurgical procedure, to REDCap.

13.5.3 CSF sampling intra-operatively, as indicated above (see section 13.2) for tumor marker (AFP and HCGβ)_ studies cytology and optional MiRNAs.

13.5.4 Tumor Specimen Submission:

Maximal tumor tissue should be sent UNFIXED to the institutional pathologist for histological diagnosis. See section 14.8.2 for more information regarding the submission of tissue samples.

14.0 NEUROPATHOLOGY GUIDELINES

Intracranial germ cell tumors do not differ histologically from those germ cell tumors arising extra-neurally. Thus, the same diagnostic criteria can be applied, and the tumors classified according to World Health Organization classification.

In most cases, the histologic diagnosis can be affirmed by conventional light microscopy. However, in some cases it is necessary to perform established adjunctive investigations, including immunohistochemistry.

14.1 Criteria for Diagnosis of Germinoma

Microscopic appearance:

Tumor composed of large round, oval or polygonal cells with abundant clear cytoplasm and large round nuclei with prominent nucleoli. These cells are arranged in nests separated by bands of fibrous tissue in which numerous lymphocytes are identified. Foci of necrosis are present and syncytial giant cells may be seen. These tumor cells are positive for placental alkaline phosphatase.

All such patients with pure germinoma will be eligible for enrollment on this study.

14.2 Criteria for Diagnosis of Immature Teratoma

Immature teratomas will be graded according to the classification of Gonzales-Cruzi:

Grade I: Less than 10% immature tissue with 90% mature elements
Grade II: Between 10% and 50% immature elements
Grade III: Greater than 50% immature elements

Immature teratomas may not have any foci (even microscopic) of germinoma, yolk sac tumor, embryonal carcinoma, choriocarcinoma, squamous carcinoma, primitive neuroectodermal tumor or adenocarcinoma. Any such foci alter the classification to teratoma with malignant elements.

Pure immature teratomas, without a pure germinoma or other mixed malignant component, will not be eligible for enrollment on this study.

14.3 Criteria for Diagnosis of Mature Teratoma

Mature teratoma will be graded according to the classification of Gonzales-Cruzi:

Mature teratoma (Grade 0): No immature elements. 100% mature tissue.

Mature teratomas may not have any foci (even microscopic) of germinoma, yolk sac tumor, embryonal carcinoma, choriocarcinoma, squamous carcinoma, primitive neuroectodermal tumor or adenocarcinoma. Any such foci alter the classification to teratoma with malignant elements.

Pure mature teratomas, without a pure germinoma or other malignant components will not be eligible for enrollment on this study.

14.3.1 Criteria for diagnosis of Growing Teratoma Syndrome

Growing teratoma syndrome (GTS) is the term applied to an enlarging intracranial germ cell tumor size during or after chemotherapy with histology of mature teratoma in the resected tumor specimen. The mass shows enlargement in the presence of normalization of initially elevated serum and/or CSF tumor markers.

14.4 Criteria for Diagnosis of Teratoma with Malignant Elements

Any teratoma in which a microscopic focus of malignancy exists, be it either malignant germ cell tumor or teratoma with foci of primitive neuroectodermal tissue or squamous carcinoma, will be characterized as malignant. Only patients with teratoma combined with germinoma or mixed malignant germ cell tumor will be eligible for enrollment on this study.

14.5 Criteria for Diagnosis of Endodermal Sinus Tumor (Yolk Sac Tumor)

Tumor composed of:

A. Small pale cells with scanty cytoplasm and round to oval nuclei with small, in apparent nucleoli. These cells are arranged in: 1) a loose microcytic pattern, 2) in solid sheets, or 3) in gland-like structures lined by a single layer of cells (polyvitelline pattern).

B. Or cells with slightly larger nuclei, which frequently have moderately prominent nucleoli. These cells are arranged into tubulopapillary structures with at least a few Schiller-Duval bodies. (Schiller-Duval bodies not usually present in microcystic, solid, or polyvitelline patterns.)

A loose, frequently myxoid, or vascular stroma.

Intracytoplasmic and extracellular hyaline globules and strands, which stain positively with PAS and are resistant to diastase digestion.

The criteria listed above are the essential features necessary for a diagnosis of yolk sac tumor. Immunohistochemical or immunoflourescent demonstration of alpha-fetoprotein and/or alpha-1-antitrypsin in the PAS positive globular material would be an interesting additional piece of information, but is not necessary for the diagnosis, since most globules do not contain either protein. Alpha-fetoprotein (if looked for) should be present in at least some of the cells.

All patients with CNS GCT containing elements of endodermal sinus tumor (yolk sac tumor) will be eligible for enrollment on this study.

14.6 Criteria for Diagnosis of Embryonal Carcinoma

Microscopic appearance:

Tumor composed of:

Sheets of large epithelial-like cells with round to irregularly oval nuclei containing one or more large nucleoli and having a coarse nuclear membrane. The cells may vary considerably in size and shape and contain abundant cytoplasm.

Cells may assume a tubulopapillary arrangement in foci, but must not be associated with intracytoplasmic and extracellular hyaline globules and strands, which are PAS positive, diastase resistant. (These latter findings are characteristic of yolk sac tumors).

Tumors will usually have large foci of necrosis, frequently occupying a central location within sheets of cells. Some necrotic cells may resemble the hyaline globules seen in yolk sac tumors, but can generally be differentiated by their location in association with dying cells.

A few embryoid bodies may be present. (NOTE: If tumor is composed solely or predominantly of embryoid bodies, then it should be classified as a polyembryoma.)

The stroma may vary from loose and edematous, to fibrous, to occasionally quite cellular.

Immunohistochemical staining of tumor tissue for CD-30 reactivity should be routinely performed as this marker has high specificity for embryonal carcinoma.

All patients with CNS GCT containing elements of embryonal carcinoma will be eligible for enrollment on this study.

14.7 Criteria for Diagnosis of Choriocarcinoma

Gross tumor composed primarily of hemorrhagic, friable tissue, with or without a few patches of grayish-white tissue.

Microscopic appearance:

Tumor composed of two cell types: the syncytiotrophoblast and the cytotrophoblast. The syncytiotrophoblast is a large, somewhat bizarre cell, with one too many hyperchromatic nuclei and generally abundant eosinophilic cytoplasm, which may or may not be vacuolated. The cytotrophoblast is present in closely packed nests and is a medium-sized, relatively uniform cell with clear cytoplasm, distinct cell margins and a vesicular nucleus. These two cell types must both be present, as individual syncytiotrophoblasts (positive for the HCGβ) may be seen in any of the malignant germ cell tumors. Patients with CNS GCT containing elements of choriocarcinoma, will be eligible for enrollment on this study.

14.8 Minimal Required Studies (only if tumor tissue of recurrence obtained)

14.8.1 Pathology Studies:

- Routine histology on paraffin sections stained with hematoxylin and eosin (H & E), periodic acid Schiff's (PAS) reagent, and reticulin stain.
- Immunohistochemistry, using antibodies against AFP, HCGβ, PLAP (placental alkaline phosphatase), c-kit (CD119), OKT4 and CD30.
- For differential diagnosis from non-germ cell tumors, it may be necessary to include antibodies against different types of intermediate filaments (e.g. vimentin, cytokeratins, desmin, GFAP, neurofilament proteins).

14.8.2 Submission of Tissue Samples

The neuropathologist at each participating institution should submit the following to Nationwide Children's Hospital:

- Copies of the Institutional Pathology Reports uploaded to REDCap (from tumor specimen obtained at the time of recurrence)
- Specimen Transmittal Form
- All paraffin embedded tissue blocks with tumor. From these blocks the NCH Neuropathologist will prepare slides, as detailed below, and then return the blocks to the submitting institution:
- H & E stained slide of each representative lesion.
- AFP, HCGβ, PLAP, and other stained slides, as indicated.
- If paraffin embedded blocks are not available for submission to the Pathology Center, then the following pathological samples are ESSENTIAL FOR PROTOCOL COMPLIANCE, and should be forwarded to the Pathology Center:
  1. One H & E stained slide for each representative lesion.
  2. Six unstained slides of tumor per block.

Biopathology Center
Nationwide Children's Hospital,
700 Children's Drive, Room WA1340
Columbus, Ohio, 43205, USA
Telephone: (001) 614-722-2894
FAX: (001) 614-722-2897
Email: BPCBank@nationwidechildrens.org

ATTN: Gempox protocol-FINLAY (Boue)

14.8.3 Cerebrospinal Fluid Samples for Biology Study:

At the time of routine, study required lumbar punctures (performed for cytology and tumor markers) an additional 1.0 ml of CSF should be collected provided appropriate informed consent has been obtained to do so.

A volume of 1.0 ml CSF should be collected and spun down (Cytospin) at the treating institution and the supernatant frozen by the treating institution. This is requested to enable testing, in the laboratory of Dr. Jeffrey Leonard at NCH, for exosomal microRNAs in the supernatant (without interference from cell proteins and RNA). Many institutions routinely add bovine serum albumin (BSA) to the CSF sample prior to centrifugation; in this case, we request that a second CSF sample be spun down without addition of albumin, for submission.

Submit frozen CSF supernatant on dry ice to:
Biopathology Center
Nationwide Children's Hospital,
700 Children's Drive, Room WA1340
Columbus, Ohio, 43205, USA
Telephone: (001) 614-722-2894
FAX: (001) 614-722-2897 Email: BPCBank@nationwidechildrens.org

ATTN: Gempox protocol-FINLAY (Leonard Lab)

14.9 Central Pathology Review Process

14.9.1 Primary Review by Study Neuropathologist:

All materials submitted from the individual institutions will be collected and collated at Nationwide Children's Hospital. Neuropathology Review will occur at time of receipt by the Primary Review Neuropathologist, Dr. Daniel Boue.

Biopathology Center
Nationwide Children's Hospital,
700 Children's Drive, Room WA1340,
Columbus, Ohio, 43205, USA
Telephone: (001) 614-722-2894
FAX: (001) 614-722-2897
Email: BPCBank@nationwidechildrens.org

ATTN: Gempox protocol-FINLAY (Boue)

14.9.2 Final Neuropathology Report

Upon conclusion of the NCH Neuropathology Review process, a final report will be sent to the institutional neuropathologist. The process of collection of samples and the review process are intended to assure accuracy of diagnosis in preference to rapid turnover time. If the final review of a case results in the opinion that the original histological diagnosis represented a protocol deviation, then the study neuropathologist will communicate this information to the Study Operations Office.

15.0 NEURORADIOLOGY GUIDELINES

15.1 MRI Scanning

There is no single best radiological examination for primary CNS germ cell tumors. MRI is superior to CT scanning in the posterior fossa, due to the lack of Hounsfield artifact from the petrous bones. There is, however, artifact in the brain stem and temporal lobes from basilar artery pulsations and CSF flow, if motion suppression techniques are not utilized. MRI is also more sensitive than CT scanning in detecting increased water content in tumor bearing tissue, but this is very non-specific when one considers that most pathological processes, including peri-tumoral vasogenic edema, increase water content. Furthermore, enhancing tumor is not adequately imaged on non-contrast MRI, that is, without intravenous gadolinium DTPA (Gd-DTPA). MRI is also insensitive to small calcifications.

15.1.1 On Study Examinations

- A pre- and post-contrast MRI scan post-operatively is mandatory for study entry. The institutional reports of these scans, and a copy of the Initial Neuro-radiology Report Form, are to be uploaded to REDCap.

- An MRI of the entire spine with and without gadolinium is mandatory for study entry. The institutional reports of these studies are to be uploaded to REDCap.

15.1.2 Follow-Up Examinations

Minimum requirement for follow-up studies is an MRI scan with and without gadolinium-DTPA.

15.1.3 Reference Scans

The reference scan is the post-operative scan obtained at the time of on-study evaluation, unless a subsequent scan demonstrates decreased tumor volume. Then the scan with the smallest tumor mass will become the reference scan. It is essential that the same imaging technique is used and compared, and that all cuts used for comparison, are in the same plane as those of the reference scan.

15.1.4 Disease Progression/Off Protocol Status

At the time of disease progression, the appropriate radiographic reports and the Follow-up Neuroradiology Report Form will be uploaded to REDCap.

15.2 Scan Parameters

15.2.1 MRI Scan of Brain

Both short (T1 weighted) and long (T2 weighted) TR sequences are essential. Plane section and TR sequences will be dependent on location of the tumor. The minimum examinations are:

- midline posterior fossa tumors - sagittal T1, axial T2, axial FLAIR

- lateral posterior fossa tumors - axial T1, axial T2, axial FLAIR
- suprasellar/hypothalamic tumors - sagittal T1, coronal T1, T2 and FLAIR
- other supratentorial tumors - coronal T1, axial T1,T2 and FLAIR
- For brainstem and temporal lobe tumors, motion suppression techniques such as cardiac gating and/or flow compensation, are recommended.

15.2.2 MRI Scan of Spine

A T1 weighted sequence should be obtained in the sagittal plane, 3mm thickness, with no interslice gap. This must be repeated with gadolinium. Axial T1 weighted images with gadolinium enhancement should be obtained for the upper cervical spine, conus, dorsal sac, and any areas of abnormality seen in sagittal imaging.

15.2.3 Use of Contrast

An additional post Gd-DTPA T1 sequence comparable to the pre-contrast T1 sequence is mandated for all MRI studies.

15.3 Timing of Radiologic Studies

15.3.1 Head MRI scans:

Head MRI scans must be obtained at the following times, and the institutional neuroradiology reports uploaded to REDCap at the completion of protocol-specified chemotherapy, along with the Neuroradiology Follow-up Form:

- Pre Induction/study entry [pre and post-op if surgery].
- Following second induction cycle.
- Post Induction (which is also pre-surgery if second look surgery is indicated).
- Post Second Surgery (either within 72 hours of surgery OR within 10-21 days after surgery)
- Post-consolidation
- Post Radiation therapy (if the patient is treated with Radiation therapy).
- At the time of progressive disease or relapse.
- At three month intervals, following completion of protocol-specified chemotherapy, for the first year from diagnosis.
- At four month intervals during the second year from diagnosis.
- At six month intervals during the third through fifth years from diagnosis.
- Annually following completion of five years from diagnosis.

Clinical management may dictate more frequent examinations.

15.3.2 Spine MRI

Spine MRI scans must be obtained at the following times, and the institutional neuroradiology reports uploaded to REDCap at the completion of protocol-specified chemotherapy, along with the Neuroradiology Follow-up Form:

- Pre Induction/study entry [pre and post-op if surgery].
- Following second induction cycle ONLY if positive at the time of study entry.
- Post induction (which will serve as pre-surgery if second look surgery is planned or pre-consolidation if the consolidation cycle is started within 4 weeks from the study).
- Post Second Surgery (either prior to surgery or within 72 hours of surgery OR within 21 days after surgery)
- Post-consolidation
- Post Radiation therapy (if the patient is treated with Radiation therapy).
- At the time of progressive disease or relapse.
- At three month intervals, following completion of protocol-specified chemotherapy, for the first year from diagnosis only if previously positive.
- At four month intervals during the second year from diagnosis only if previously positive.
- At six month intervals during the third through fifth years from diagnosis only if previously positive.
- Annually following completion of five years from diagnosis only if previously positive.

Clinical management may dictate more frequent examinations.

15.4 Centralized Neuroradiology Review

A process of centralized review of neuroradiological studies will be undertaken at Nationwide Children's Hospital. The study Neuroradiologists or Nicholas Zumberg in conjunction with the study P.I., Dr. Jonathan Finlay will review the radiology and report their summary to the DSMB .

All CD copies of MRI scans requested for central neuroradiology submission will be stored in locked secure areas with research staff access only.

Address for Submission of Reports and Scans

Dr. Jonathan Finlay, MB, Ch.B.
Nationwide Children's Hospital
700 Children's Dr. Room ED544
Columbus, Ohio 43205
jonathan.finlay@nationwidechildrens.org

16.0 RADIATION THERAPY GUIDELINES

Since response to radiation therapy is neither a primary nor a secondary aim of the study, and since a majority of patients with MMGCT might have previously received some form of irradiation, the guidelines to administer radiation therapy at the time of relapse will be left to the discretion of the treating oncologist.

17.0 DATA SAFETY AND MONITORING PLAN

The "GemPOx" Clinical Trials Data Safety Monitoring Board (DSMB) will act in an advisory capacity to the Principal Investigator this study. Monitoring will occur every six months (and more frequently as needed) from the date the study is opened at Nationwide Children's Hospital. Reports to the Data Safety and Monitoring Board will include the following information:

1. Accruals
2. Responses
3. Adverse events and evidence of reporting to appropriate review committees

The responsibility of the DSMB is to review the research protocol, inform consent and plans for data safety monitoring during the entire course of the study. This committee will evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, trial site performance and other factors that may have impact on participant outcomes. This DSMB will follow the Hem/Onc/BMT Data Safety Monitoring Board Charter.

17.1 Study Monitoring and Adverse Event Reporting

The monitoring of study data is an ongoing process by the DSMB The data for each patient (eligibility, evaluability and course by course) is submitted from the GemPOx sites via the electronic case report forms (eCRF's) built into the database system (REDCap) hosted by NCH. Adverse events will be reported to the NCH using the eCRF's according to Section 18.0.

The DSMB will have a timetable in which to review the accumulating data (adverse events, treatment records, disease assessments, specimen collection, last follow-up and other protocol specific data) for completeness and consistency. Data queries are generated via email to the Institutional Clinical Research Coordinators (CRCs) using the GemPOx Data Query Form to resolve incomplete data, data inconsistencies or errors identified while verifying eligibility data, and evaluability data. Data review and corresponding queries also occur at the completion of each course of therapy, when patients cease treatment, and when patients are off study. The PI must sign-off on all data submitted for eligibility, evaluability, and each protocol course via a web-based sign-off system. The subsequent 'freeze' of data records is on a per-patient, prospective, course by course basis.

All serious adverse events (SAEs) will be immediately (within 24 hours of knowledge of the event) reported by site personnel according to the protocol specifications that shall include notification of the protocol study PI, DSMB, local IRB. Refer to Section 18.0 for Adverse Event Reporting.

17.2 Reviews by Protocol Chairs and Co-Chairs

The PI is required to review and confirm that all interpretations are consistent with the protocol on which the patient is treated. The Lead Data Clinical Research Coordinator works with the PI to resolve any data questions that may arise. Reports of the accumulating data including patient accrual and status, along with toxicities will be available to PI and co-chairs over the Internet via a secure, encrypted connection to the server. These will be updated daily. Access to this site is recorded to track protocol study chair monitoring.

17.3 Automated Data Delinquency Reporting System

The GemPOx sites are expected to enter patient data in the database within the timelines specified per MOP. The Lead Data Clinical Research Coordinator and PI are expected to review the data and sign-off according to MOP specifications. The Lead Data Clinical Research Coordinator utilizes e-mail data delinquency reminders to remind the member sites' CRCs, site attending physicians and protocol study chairs of the expected data entry per the specified timetable.

1. Data deficiency reminders corresponding to eligibility and evaluability
GemPOx sites are expected to provide complete eligibility and evaluability data within specified time lines detailed in the MOP. Notifications that the data are incomplete are automatically sent to the site and include the date that all issues must be resolved. Failure to comply by the specified date will result in suspension of all institutional registration privileges.

2. Data deficiency reminders corresponding to course data.
GemPOx sites are expected to provide complete course data within specified timelines. Notifications that the data are incomplete are automatically sent to the site. Missing data elements are identified in the report.

17.4 Semi-annual GemPOx Meeting Minutes

Protocol summary reports of patient accrual, eligibility, toxicity and other study objectives are generated semi-annually by the DSMB and distributed via the SharePoint website. The reports will be a collaborative effort of the Lead Data Clinical Research Coordinator, study statistician, PI, correlative study investigators, and other protocol collaborators. Outcome data are not reported until released by the GemPOx DSMB.

17.5 Auditing and Subsites

Audits are conducted as needed to document the accuracy of data submitted and to verify investigator compliance with protocol and regulatory requirements. Auditing is accomplished by verifying against the institution's source documents patient data, eligibility and consent information submitted to Nationwide Children's Hospital via eCRFs. Additionally, IRB documentation is reviewed.

17.6 Data, Safety Monitoring Board (DSMB) Membership

The Chair of the GemPOx Steering Committee shall appoint a senior neuro-oncology investigator to chair the DSMB; additional members shall be identified in consultation with the DSMB Chair and appointed by the Chair of the GemPOx. A minimum of 5 voting members shall comprise the DSMB, including (1) the Chair, (2) a physician member of GemPOx Committee, (3) a pediatric oncologist, a biostatistician, and a radiation oncologist who is not an investigator at GemPOx institution. The additional member(s) shall be appointed such that a majority of the voting members are from outside the Consortium and the Board includes at least two neuro-oncologists trained in pediatric oncology or neurology. Appointments will be for 3-4 year terms, renewable once by the Chair of GemPOx. Any member of the DSMB shall excuse himself or herself from discussion of any protocol for which they have a perceived conflict of interest. All members

of the DSMB will complete the GemPOx conflict of interest disclosure forms at least annually. Premature disclosure of confidential DSMB discussions by members of the GemPOx DSMB will result in censure of that member by the GemPOx Steering Committee in accordance with the GemPOx Charter

17.7 Meetings

The DSMB shall convene at least twice each year by telephone conference\ At other times, the DSMB chair shall utilize electronic communication or scheduled telephone conferencing at his/her discretion in continuing the responsibilities of the DSMB. The DSMB will establish committee procedures; all decisions of the DSMB must reflect participation of a majority of the committee's member. Decisions of the DSMB may be rendered during any of the aforementioned sessions or by electronic voting of the membership. Any GemPOx investigator can request that the Chair of the DSMB convene a teleconference call to discuss a specific GemPOx protocol.

17.8 DSMB Decisions and Recommendations

Decisions and recommendations of the DSMB will be approved by the Chair of the DSMB then forwarded to the committee members.

1. Comments requiring an immediate response
The GemPOx study chair will be responsible for responses requiring an immediate response. PI and biostatisticians may be asked to assist in the response. The responses will be sent to the DSMB within six weeks from receipt of the comments by the PI.

2. Comments requiring responses for the next DSMC meeting
Protocol specific comments will be sent to the GemPOx study chair. Responses are requested within four weeks. PI and biostatisticians may assist the protocol study chairs with responses concerning data issues if requested.

18.0 REPORTING OF ADVERSE EVENTS AND TOXICITIES/ADVERSE EVENT CRITERIA

Toxicities are reported in a routine manner at scheduled times during a trial. These routine reporting requirements are provided in the MOP. Certain events must be reported in an expedited manner to allow for timely monitoring of patient safety and care.

18.1 Routine Toxicity Reporting

Toxicities will be graded according to the CTCAE criteria, version 4.0. The site, measure, and grade for all Grade 3 and higher toxicities are to be reported on the appropriate data collection forms and submitted within 2 weeks of the completion of each cycle of therapy. CTC AE version 4.0 may be downloaded from the CTEP web site (http://ctep.cancer.gov).

18.2 Guidelines for Reporting Adverse Drug Reactions for Commercial Agents in an Expedited Manner

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In GemPOx all of the agents used are commercially available.

18.3 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

Determination of Reporting Requirements includes the following considerations: 1) the characteristics of the adverse event including the *grade* (severity); 2) the *relationship to the study therapy* (attribution); and 3) the *prior experience* (expectedness) of the adverse event.

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for reporting purposes only, when either the type of event or the severity of the event is not listed in: the current known toxicities for each commercial agent as provided in the Drug Information Section of this protocol; or the drug package insert (for treatments with commercially available agents).

Routine Adverse Event Reporting:
Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database, REDCap. For this study, routine reporting will include all Grade 3 and higher Adverse Events.

Serious Adverse Events Reporting:

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

1) Death
2) A life-threatening adverse event
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations which are part of routine medical practice
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) 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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

Use the GemPOx protocol-specific patient ID provided during trial registration on SAE forms. The SAE form is located in the "GemPOx" REDCap database.

Attribution	Grade 4 Report to Nationwide Children's Hospital by fax **614-722-4635** within 3 days of occurrence.		Grade 5* Report to Nationwide Children's Hospital by fax **614-722-4635** within 24 hours of occurrence.	
	Unexpected	**Expected**	**Unexpected**	**Expected**
Unrelated or Unlikely	**Not required**	**Not required**	**REDCap**	**REDCap**
Possible, Probable, Definite	**REDCap**	**REDCap**	**REDCap**	**REDCap**
*This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported.				

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Appendix I

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be multiples of 10			
Karnofsky		**Lansky***	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on Normal activity or do active work.	70	Both greater restriction of and less Time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; Keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

Appendix II

Anticonvulsant <u>ELIGIBLE</u> Not or minimal enzyme inducing	
Generic Name	*Trade Name*
Gabapentin	Neurontin
Lamotrigine	Lamictal
Levetiracetam	Keppra
Tigabine	Gabitril
Topiramate	Topamax
Valproic Acid	Depakote, Depakene
Zonisamide	Zonegran
Enzyme inducing anticonvulsant drugs (EIACD): <u>NOT ELIGIBLE</u>	
Generic Name	*Trade Name*
Carbamazepine	Tegretol
Felbamate	Felbatol
Phenobarbital	Phenobarbital
Phenytoin	Dilantin
Primidone	Mysoline
Oxcarbazepine	Trileptal

GemPOx Induction for Recurrent or Progressive CNS Germ Cell Tumor
Diagnosis:
Name _____ Provider _____
MRN _____
DOB _____

Induction	Weight kg	Height cm	BSA m^2

Cycle length 14 days, planned for maximum of 4 cycles
Criteria to start each cycle: ANC 750 or greater, and platelets 75,000 or greater.

PACLitaxel	Premedicate with dexamethasone, ranitidine and diphenhydramine before paclitaxel. 170 mg/m^2/dose IV ONCE. Give on Day 1. Start at Hour 0. Infuse over 3 hours.
gemcitabine	800 mg/m^2/dose IV ONCE. Give on Day 1. Start at Hour 3. Infuse over 1 hour.
oxaliplatin	100 mg/m^2/dose IV ONCE. Give on Day 1. Start at Hour 4. Infuse over 2 hours.
optional **filgrastim**	Routine use of filgrastim during Induction is not recommended. Add if patient has a delay of 7 – 14 days in starting the next cycle due to neutropenia. 5 mcg/kg/dose subcutaneous QDAY. MAXIMUM DOSE 480 mcg Start on Day 2, at least 24 hours after oxaliplatin is completed. Continue until postnadir ANC is greater than 1000.

Date Due	Date Given	Cycle	Day	PACLitaxel	gemcitabine	oxaliplatin	filgrastim *optional*	Observations
		1	1	_____ mg	_____ mg	_____ mg		a b c d% e% h j k l
			2				_____ mcg	
			8				↓	d% e%
			14					
		2	1	_____ mg	_____ mg	_____ mg		a b c d% e%
			2				_____ mcg	
			8				↓	d% e%
			14	After Cycle 2 is completed, if in CR, then proceed to Consolidation. If less than CR, then give 2 more cycles of Induction				a c d% e% h j k l
		3	1	_____ mg	_____ mg	_____ mg		a b c d% e%
			2				_____ mcg	
			8				↓	d% e%
			14					
		4	1	_____ mg	_____ mg	_____ mg		a b c d% e%
			2				_____ mcg	
			8				↓	d% e%
			14	After Cycle 4 is completed, perform extent of disease evaluation				a c d% e% j k l

Observations

a. height, weight, BSA

b. HCG, urine qualitative for females of childbearing potential

c. blood for alpha-1-fetoprotein, tumor and BHCG, tumor marker
Obtain around same time when CSF markers are obtained

d. CBC with automated diff, reflex to manual.
% Obtain weekly

e. ALT, AST, bilirubin, BUN, creatinine, electrolytes, glucose, calcium, magnesium, phosphorous.
% Obtain weekly

f. Urinalysis

g. Endocrine evaluation
free T4, TSH, IGF1, IGFBP3, LH (males over age 10, females over age 9),
FSH (males over age 10, females over age 9), testosterone (males over age 10),
estradiol (females over age 9), Tanner stage, cortisol at 8 AM, BUN, creatinine, electrolytes, and urine specific gravity on first morning void.
If any endocrine parameter is abnormal, then referral to a pediatric endocrinologist for further evaluation, dynamic testing, and treatment is required.

h. Audiology evaluation

i. Creatinine clearance or GFR renal scan

j. MRI Brain and Spine

k. lumbar puncture for Cytology, cell count CSF, alpha-1-fetoprotein, tumor, and BHCG, tumor marker

l. lumbar puncture for CSF microRNA study (*optional*). See section 14.8.3

GemPOx Consolidation for Recurrent or Progressive CNS Germ Cell Tumor
Diagnosis:
Name _____ Provider _____
MRN _____
DOB _____

Consolidation	Weight kg	Height cm	BSA m^2

Cycle length 42 days, planned for 1 cycle
Criteria to start each cycle: ANC 750 or greater, and platelets 75,000 or greater.

CARBOplatin	Calculate dose using both the Calvert formula and body size. **Use the LOWER DOSE from the CALVERT FORMULA or the MAXIMUM DOSE** **CALVERT FORMULA** based on age with target AUC = 7 mg•min/mL Dose calculated with the Calvert formula is the **total dose in milligrams**, not mg/ m^2. AGE 0 to 9.99 years carboplatin total dose in **mg** = 7 x **[** (GFR in mL/min) + (0.36 x weight in kg) **]** AGE 10 years and above Maximum GFR 125 mL/min carboplatin total dose in **mg** = 7 x **[** (GFR in mL/min) + 25 **]** **MAXIMUM DOSE** AGE 0 to 2.99 years 16.7 mg/kg/dose IV QDAY for 3 doses AGE 3 years and above 500 mg/m^2/dose IV QDAY for 3 doses Give on Days –8, –7 and –6. Start at Hour 0. Infuse over 4 hours.
thiotepa	AGE 0 to 2.99 years 10 mg/kg/dose IV QDAY for 3 doses AGE 3 years and above 300 mg/m^2/dose IV QDAY for 3 doses Give on Days –5, –4 and –3. Start at Hour 0. Infuse over 3 hours
etoposide	AGE 0 to 2.99 years 8.3 mg/kg/dose IV QDAY for 3 doses AGE 3 years and above 250 mg/m^2/dose IV QDAY for 3 doses Give on Days –5, –4 and –3. Start at Hour 3. Infuse over 3 hours
filgrastim	5 mcg/kg/dose IV or subcutaneous QDAY. MAXIMUM DOSE 480 mcg Start on Day +1 Continue until post nadir ANC is greater than 1000 for 3 consecutive days If the ANC is less than 500 on Day +21, then increase dose to 10 mcg/kg/dose

Date Due	Date Given	Day	CARBOplatin	thiotepa	etoposide	filgrastim	Observations
		– 8	_____ mg				a b c d e f h i j k l
		– 7	_____ mg				i
		– 6	_____ mg				
		– 5		_____ mg	_____ mg		
		– 4		_____ mg	_____ mg		
		– 3		_____ mg	_____ mg		
		– 2					
		– 1					
		0	Autologous Hematopoietic Progenitor Cell Rescue				a d* e*
		+ 1				_____ mcg	
		+ 2				↓	
		+ 42					a c d e g h i j k l

Observations

a. height, weight, BSA
b. HCG, urine qualitative for females of childbearing potential
c. blood for alpha-1-fetoprotein, tumor and BHCG, tumor marker
d. CBC with automated diff, reflex to manual.
[*] Obtain at least twice weekly starting on Day 0 until engraftment.
e. ALT, AST, bilirubin, BUN, creatinine, electrolytes, glucose, calcium, magnesium, phosphorous.
[*] Obtain at least twice weekly starting on Day 0 until engraftment.
f. Urinalysis
g. Endocrine evaluation
free T4, TSH, IGF1, IGFBP3, LH (males over age 10, females over age 9),
FSH (males over age 10, females over age 9), testosterone (males over age 10),
estradiol (females over age 9), Tanner stage, cortisol at 8 AM, BUN, creatinine, electrolytes, and urine specific gravity on first morning void.
If any endocrine parameter is abnormal, then referral to a pediatric endocrinologist for further evaluation, dynamic testing, and treatment is required.
h. Audiology evaluation
i. Creatinine clearance or GFR renal scan
j. MRI Brain and Spine
k. lumbar puncture for Cytology, cell count CSF, alpha-1-fetoprotein, tumor, and BHCG, tumor marker
l. lumbar puncture for CSF microRNA study (*optional*). See section 14.8.3