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PBMTC ONC-032: High dose temozolomide, thiotepa and carboplatin with autologous stem cell rescue (ASCR) followed by continuation therapy with 13-cis-retinoic acid in patients with recurrent/refractory malignant brain tumors.

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1.0 SPECIFIC AIMS

1.1 Primary

- To assess the event-free survival (EFS) and overall survival (OS) of patients with recurrent or refractory medulloblastoma/ primitive neuroectodermal tumors (PNET) with minimal residual disease treated with high dose temozolomide, thiotepa and carboplatin with ASCR followed by continuation therapy with 13-cis-retinoic acid.

1.2 Secondary

- To assess the EFS and OS of patients with recurrent or refractory central nervous system germ cell tumor (CNS GCT), high grade glioma, brainstem glioma, ependymoma, atypical teratoid/rhabdoid tumor (AT/RT) and other high grade malignant brain tumors (excluding high grade gliomas) with minimal residual disease treated with high dose temozolomide, thiotepa and carboplatin with ASCR followed by continuation therapy with 13-cis-retinoic acid.
- To evaluate the toxicity of high dose temozolomide, thiotepa and carboplatin with ASCR when performed in a multi-institutional setting.
- To evaluate the toxicity of 13-cis-retinoic acid following high dose temozolomide, thiotepa and carboplatin with ASCR.
- To assess the inter-individual variability in plasma pharmacokinetics of 13-cis-retinoic acid and assess a single CSF 13-cis-retinoic acid level to determine if it is a potential indicator of CNS penetration of the drug.
- To investigate the influence of genetic variation in enzymes involved in the metabolism of 13-cis-retinoic acid on the pharmacokinetics of this agent.
- To relate inter-individual variability in the pharmacokinetics of 13-cis-retinoic acid and genetic variation to clinical response as measured by event-free survival and toxicity.

2.0 EXPERIMENTAL DESIGN

This is a phase II study of temozolomide, thiotepa and carboplatin with ASCR followed by continuation therapy with 13-cis-retinoic acid in patients with recurrent or refractory brain tumors with minimal residual disease. Patients will first undergo the collection of autologous peripheral blood stem cells following mobilization with filgrastim and/or chemotherapy. Cytoreductive therapy will begin after adequate numbers of stem cells have been collected. Patients will receive temozolomide orally twice daily for five days followed by thiotepa and carboplatin administered intravenously daily for three days. Autologous stem cells will be reinfused three days following the completion of the chemotherapy. Patients who have not already received their life time maximum dose of radiation therapy may receive additional radiation therapy following recovery from the high dose chemotherapy. Patients will begin therapy with 13-cis-retinoic acid between day +42 and day +77 following ASCR. The 13-cis-retinoic acid will be given daily for 14 days followed by a 14 day break for six months.

Patients will be encouraged to have blood and CSF obtained at specific time points around the first course of 13-cis-retinoic acid to determine blood and CSF pharmacokinetics of 13-cis-retinoic acid and genetic variation in enzymes involved in the metabolism of 13-cis-retinoic acid. There will be centralized review of pathology and response data.

3.0 BACKGROUND AND RATIONALE

3.1 General Background

Patients with recurrent malignant brain tumors have a dismal prognosis[1,2,3,4,5]. The use of conventional dose chemotherapy in these patients can produce objective radiographic responses, but almost invariably of duration measured in months rather than years. The use of high dose chemotherapy with autologous stem cell

rescue for the treatment of patients with recurrent malignant brain tumors has been reported from several centers. Responses have been observed in patients with recurrent medulloblastoma, PNET, high grade glioma and CNS GCT.[6,7,8,9,10] These regimens are most efficacious in patients with minimal residual tumor burden at the time of the high dose chemotherapy. However, event-free survival ranging from approximately 15% (recurrent glioblastoma multiforme) to 30% (recurrent medulloblastoma)[7,6] remains poor and begs the question whether further chemotherapeutic intensification and the addition of new agents could increase the proportion of patients achieving durable survival without increasing the early morbidity and mortality of such treatment.

3.2 Rationale for the use of temozolomide, thiotepa and carboplatin

Although many different myeloablative preparative regimens have been utilized in recurrent CNS tumors, one of the most successful regimens includes high dose thiotepa, carboplatin and etoposide. This regimen was utilized in CCG 9883 and resulted in a 30% 3 year EFS for patients with recurrent medulloblastoma/PNET, but it also resulted in significant toxicity with a 13% toxic death rate[7]. In an attempt to potentially decrease the toxicity and possibly improve the efficacy of this regimen for recurrent CNS tumors, Gardner et. al (New York University) have substituted temozolomide for etoposide in combination with thiotepa and carboplatin in a phase I dose escalation study. Dose limiting toxicity was seen with a dose of temozolomide of 200 mg/m2/dose bid (400 mg/m2/day). The dose limiting toxicity included one patient with severe mucositis and a second patient with transient encephalopathy. The dose of temozolomide for the phase II study is 350 mg/m2/day (175 mg/m2/dose) x 5 days.

Temozolomide is a new oral alkylating agent. At physiologic pH, temozolomide spontaneously degrades to MTIC which is the active catabolite of dacarbazine (DTIC).[11] Temozolomide exerts its primary activity by adding a methyl group to the O^6-position of guanine. O^6-alkylguanine DNA alkyl transferase (AGT) repairs the damage caused by methylation of guanine. Temozolomide, like the nitrosoureas, is more effective in tumors with low levels of AGT.[12] Gerson et al. found that the administration of temozolomide in a twice daily schedule rapidly depleted AGT in a dose dependent fashion and prevented its regeneration.[13]

The Children's Cancer Group performed a phase I study of temozolomide in pediatric patients with recurrent solid tumors.[14] The dose of temozolomide was stratified by prior craniospinal irradiation and was administered orally for five days with subsequent cycles administered every 21 to 28 days. The maximum tolerated dose was 215 mg/m^2/day for patients without prior craniospinal irradiation and 180 mg/m^2/day for those with prior craniospinal irradiation. The dose limiting toxicities were neutropenia and thrombocytopenia. Although no nonhematologic dose limiting toxicity occurred, more than half of the patients had nausea and vomiting. The United Kingdom has also published results of a phase I study of temozolomide in pediatric patients with advanced cancer where the dose limiting toxicity was myelosuppression[15].

Temozolomide has been found to have efficacy in the treatment of high-grade gliomas in adults. In a phase II study by Newlands et al, temozolomide was initially given at a dose of 150 mg/m^2/day for five days to adult patients with malignant gliomas.[16] The dose was increased to 200 mg/m^2/day for 5 days in subsequent courses if there was no significant myelosuppression noted on day 22. The objective response rate was 30% in 27 patients with primary disease treated with two courses of temozolomide prior to radiotherapy and 25% in 48 patients who were treated after their disease had recurred following initial surgery and radiotherapy. In a multicenter phase II trial of temozolomide in adult patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse, the objective response rate was 35% (8% complete response (CR), 27% partial response (PR)) with an additional 26% of patients with stable disease (SD).[17] Furthermore, the CR, PR, and SD were associated with health-related quality-of-life benefits.

There is some experience using temozolomide in pediatric patients with malignant brain tumors, including medulloblastoma/PNET. Friedman et al. have demonstrated efficacy of temozolomide against medulloblastoma tumor xenografts[18]. A pediatric phase II study of temozolomide in recurrent pediatric CNS tumors (CCG A09701) showed activity of temozolomide in recurrent medulloblastoma/PNET resulting in a CR in 1/21, PR in 3/21 and SD in 1/21 patients. A single case report describes a complete response of leptomeningeal recurrence of medulloblastoma to temozolomide[19].

3.3 Rationale for continuation therapy with 13-cis-retinoic acid

Despite encouraging preliminary results with myeloablative chemotherapy followed by stem cell transplant, the majority of patients succumb to their tumor due to residual microscopic disease that is resistant to chemotherapy and radiation therapy. It would be appealing to find a biological agent for recurrent brain tumors that could be utilized post transplant to eliminate or change the aggressive potential of any minimal residual disease. 13-cis-retinoic acid is a well known biological agent that induces differentiation and decreases proliferation of neuroblastoma cell lines. 13-cis-retinoic acid has been utilized clinically in a previous neuroblastoma treatment study, CCG 3891, where it was given post-transplant on a schedule consisting of six 28 day cycles, with 13-cis-retinoic acid administered on the first 14 days of each 28 day cycle. With this regimen, 13-cis-retinoic acid was well tolerated with mild toxicities including chelitis, dry skin, hypertriglyceridemia and hypercalcemia, and was shown to improve the EFS and OS of patients with high risk neuroblastoma.[20]

There is minimal experience using 13-cis-retinoic acid in brain tumors. Bouterfa et al. reported inhibition of proliferation and migration of primary cultures of human glioblastoma multiforme when exposed to retinoids including 13-cis-retinoic acid.[21] Yung et al. reported a Phase II study for recurrent malignant glioma utilizing 13-cis-retinoic acid at a dose of 60-100 mg/m^2/day for 21 out of 28 days. Of the forty-three patients who received more than 4 weeks of therapy, 7% had a PR, 16% had a minor response and 30% had stable disease[22]. Agrawal et al. from New York University (personal communication) have found that medulloblastoma cells express RAR-alpha but not RAR-beta by western blot. They have treated multiple established medulloblastoma cell lines and short term medulloblastoma cultures to retinoids and have found that approximately 65% respond. The medulloblastoma cell line D283 MED has been retinoid sensitive with a concomitant decrease in Hu expression, a marker of neuronal differentiation, suggesting that the antiproliferative effect of retinoids may not be associated with differentiation along a neuronal pathway. Olson et al from Fred Hutchinson Cancer Research Center has looked at in-vitro response of medulloblastoma and ependymoma cells to retinoids.[23] He found that medulloblastoma cell lines D283 and D341 underwent apoptosis in 59-78% of the cells when exposed to 13-cis-retinoic acid and all-trans retinoic acid, whereas meduloblastoma cell lines DAOY and UW228 showed no response to these agents. Olson also noted that apoptosis was inhibited in the face of retinoic acid receptor antagonists, suggesting that retinoic acid receptor activity is critical to the activity of retinoids in these cell lines. Interestingly, the subset of D282 cells that did not undergo apoptosis developed neuritic extensions thought consistent with differentiation/maturation of the cell. Olson has also tested 10 fresh primary medulloblastoma tumors and found a high rate of apoptosis in 8 of the 10 tumors. He has also studied retinoid exposure to 2 fresh primary ependymoma tumors and noted neuronal differentiation in the cells of both tumors and apoptosis in one of the tumors.

3.4 Companion Biology Study

3.4.1 Investigation of the relationship of 13-cis-retinoic acid pharmacokinetics and pharmacogenetic variation in drug metabolizing enzymes.

13-cis-retinoic acid pharmacokinetics were previously examined in a phase I study utilizing 13-cis-retinoic acid in 31 pediatric patients with neuroblastoma following BMT. This study found significant inter-patient variability in peak serum levels of 13-cis-retinoic acid.[24,25] Many things may affect the pharmacokinetics of 13-cis-retinoic acid and therefore may influence its efficacy. 13-cis-retinoic acid, when absorbed, may be subject to first-pass metabolism and subsequent plasma (and tumor) concentrations will depend on the rate of metabolism to the inactive 4-oxo metabolite.

A number of cytochrome P450 (CYP) enzymes have been identified as playing a role in the metabolism of 13-cis-retinoic acid including CYP2C8 and CYP3A7. Genetic polymorphisms in the CYP2C8 or CYP3A7 gene have been described which could underlie individual differences in 13-cis-retinoic acid metabolism and bioavailability.[26,27,28,29] A further aspect of 13-cis-retinoic acid metabolism is glucuronidation, of both the parent drug and of 4-hydroxy-metabolites. This conjugation may be mediated by UGT1A1 or UGT2B7,[30] both enzymes that are subject to genetic polymorphisms.[31]

Although limited studies have been done on the pharmacokinetics of 13-cis-retinoic acid, there are no human data and minimal animal data concerning the penetration of 13-cis-retinoic acid into the central nervous system.

13-cis-retinoic acid is very lipophilic and is highly bound (>99%) to plasma proteins.[32] Because of these features, it is uncertain how accurately CSF levels of 13-cis-retinoic acid will predict penetration of the drug into the brain tissue. There are no studies in humans or animals in regards to CSF 13-cis-retinoic acid levels. There are data in rats regarding the penetration of 13-cis-retinoic acid into brain tissue. Le Doze et al. measured the pharmacokinetics of 13-cis-retinoic acid in rat serum and brain tissue and found 13-cis-retinoic acid permeated into the rat brain. The brain tissue levels of 13-cis retinoic acid were lower than the plasma levels, but concentration-time profile seen in the brain tissue paralleled that seen in the serum.[33]

A current UK study (UKCCSG Study PK 2000 08) is investigating the variation in 13-cis-retinoic acid pharmacokinetics within and between courses of 13-cis-retinoic acid when given to neuroblastoma patients following autologous stem cell transplant. It has currently recruited 28 patients and preliminary data indicate that plasma concentrations of 4-oxo-13-cis-retinoic acid, an inactive metabolite of 13-cis-retinoic can accumulate to exceed the concentration of the parent compound during a 14 day course of treatment.[34] The data also indicate an approximate 10-fold variation in 4-oxo-13-cis-retinoic acid peak plasma concentrations between patients receiving a standard dose of 13-cis-retinoic acid. Because 4-oxo-13-cis-retinoic acid is a retinoid breakdown product with little or no activity, this level of metabolism *in vivo* may lead to a diminished efficacy of 13-cis-retinoic acid.

The current study is designed to build on data being obtained in the UK, concerning the inter-individual variability of 13-cis-retinoic acid pharmacokinetics and the influence of genetic variation in cytochrome P450 enzymes on the metabolism of 13-cis-retinoic acid. This will allow determination of potential relationships between inter-individual pharmacokinetic variability, genetic variation in enzyme activity and clinical response (3 year event-free survival) and toxicity. Results from this study will provide an insight into whether modulation of 13-cis-retinoic acid dosing according to systemic exposure and/or genotype could be used in future studies to optimize the treatment of cancers. In this study, pharmacokinetic and pharmacogenetic sampling will be carried out during a single course of 13-cis-retinoic acid treatment. Five serum samples (pre-treatment, and at 1,2,4 and 6 hours after oral administration of 13-cis-retinoic acid on day 14 of cycle 1) along with a single CSF sample (2 hours after administration of 13-cis-retinoic acid on day 14 of the first course) will be collected to assess 13-cis-retinoic acid levels. A single blood sample will be obtained pre-treatment with 13-cis-retinoic acid to perform genotype analysis for enzymes thought to be involved in the metabolism of 13-cis-retinoic acid. All patients are strongly encouraged to participate in all aspects of the pharmacokinetic/ genotype analysis study. Most patients have tumors with a propensity for CSF dissemination and thus will require a spinal tap pre-maintenance for disease analysis, which can be coordinated with the CSF pharmacokinetic level.

4.0 Patient Eligibility

4.1 Patients with recurrent or refractory medulloblastoma/PNET, CNS germ cell tumors, ependymomas, AT/RT, high grade glioma and other malignant brain tumors. Brainstem gliomas are eligible if residual disease is $\leq$ 1.5cc and if the patient is off decadron.

4.2 Patients must have recurrent or refractory disease following at least one prior course of therapy and must have minimal residual disease defined as $\leq$ 1.5 cm^2 of enhancement. Patients with + CSF cytology, linear or fine nodular leptomeningeal disease are eligible.

4.3 Karnofsky Performance Status or Lansky Performance score $\geq$ 70%.

4.4 Patients must have an anticipated life expectancy of greater than 12 weeks to be eligible for this study.

4.5 Adequate hematologic, renal, liver, and cardiac function as demonstrated by laboratory values performed within 21 days, inclusive, prior to administration of temozolomide.

- Absolute neutrophil count $\geq$ 750/mm^3
- Platelet count $\geq$ 50,000/mm^3
- Hemoglobin $\geq$ 10 gm/dL (Patients may be transfused to raise the hemoglobin above 10gm/dl)
- BUN and serum creatinine < 1.5 times upper limit of laboratory normal
- Creatinine clearance or GFR $\geq$ 70 cc/min/1.73 m^2

- Total serum bilirubin < 1.5 times upper limit of laboratory normal
- SGPT < 2.5 times upper limit of laboratory normal

4.6 Patients must have an adequate number of autologous stem cells available defined as a minimum of 2 x 10^6 CD 34+ cells/kg and preferably at least 5 x 10^6 CD 34+ cells/kg.

4.7 Age greater than 6 months of age and less than 21 years.

4.8 Patients must have recovered from any effects of major surgery, chemotherapy or radiation. Patients may not have received chemotherapy (excluding nitrosureas) within 21 days and may not have received radiation therapy or nitrosureas within 42 days of starting treatment.

4.9 Patients may have received stereotactic radiation at the time of recurrence as part of their salvage treatment.

4.10 Patients or legal guardians must give written, informed consent.

Patients with <u>any</u> of the following criteria are excluded from the study:

4.11 Previous myeloablative therapy

4.12 Frequent vomiting or medical condition that could interfere with oral medication intake (e.g., partial bowel obstruction)

4.13 Previous or concurrent malignancies at other sites with the exception of surgically cured carcinoma in-situ of the cervix and basal or squamous cell carcinoma of the skin. Patients with prior malignancies which have not required anti-tumor treatment within the preceding 24 months are eligible.

4.14 Known HIV positivity or AIDS-related illness.

4.15 Pregnant or nursing women.

4.16 Women of childbearing potential who are not using an effective method of contraception.

4.17 Men who refuse to use an effective method of contraception.

4.18 **Institutional Human Rights Committee/Institutional Review Board approval**:

Approval for the use of this treatment regimen by the individual's Human Rights Committee or Institutional Review Board (IRB) must be obtained in accordance with the individual institutional assurance policies of the United States DHHS and must be on file at the New York University Pediatric Oncology Trials Office prior to enrollment of any patient on study.

4.19 **Patient Registration:**

Patients will enter on study at the time protocol therapy is planned to begin. Eligible patients will be registered by contacting Rosa Chu in the Pediatric Oncology Clinical Trials Office at New York University Monday through Friday 9am-5pm Eastern Time at (212)263-9924 except holidays. The information requested on the protocol eligibility form must be completed and the signed informed consent for protocol therapy must be faxed to (212)263-8410 at the time of this telephone call for registration to occur. Patients must be registered prior to starting protocol therapy. An email confirming eligibility will be sent to the treating institution.

5.0 TREATMENT PLAN

5.1 Post-relapse/Pre-transplant therapy:
This therapy is not dictated by study. It may include surgery and/or chemotherapy. Radiation therapy is allowed but not recommended during reinduction because of the potential increase in transplant toxicity.

5.2 Autologous Peripheral Blood Stem Cell Collection
Patients will undergo leukapheresis prior to study entry. Patients will be required to have an adequate number of autologous stem cells available, defined as a minimum of 2 x 10^6 CD 34+ cells/kg and preferably at least 5 x 10^6 CD 34+ cells/kg. Patients who will be receiving craniospinal radiation therapy as part of their salvage treatment should attempt to undergo stem cell harvest prior to radiation therapy.

5.3 Myeloablative Chemotherapy--Temozolomide, Thiotepa, and Carboplatin.

5.3.1 **Chemotherapy will be dosed according to adjusted body weight for all patients weighing > 125% ideal weight for height. (See appendix A for calculating adjusted body weight.)**

5.3.2 ***Note: The carboplatin will be dosed using the raw creatinine clearance. However, if the corrected creatinine clearance is < 70 ml/min/1.73m^2, neither the carboplatin nor the thiotepa will be given. The study PI should be notified immediately.**

5.3.3 **Patients who have a corrected creatinine clearance ≥ 70 ml/min/1.73m^2 but < 100 ml/min/1.73m^2 will receive a lower dose of carboplatin and thiotepa than patients whose corrected creatinine clearance is ≥ 100 ml/min/1.73m^2.**

5.3.4: **The dose of temozolomide will be the same for all patients whose corrected creatinine clearance is ≥ 70 ml/min/1.73m^2.**

5.3.5: **Days -10, -9, -8, -7, and -6**
Temozolomide will be administered orally every twelve hours (total of ten doses) for five days on days -10 through -6. The dose of temozolomide is 175 mg/m^2/dose bid (or 5.8 mg/kg/dose bid for patients < 3 years of age) for 5 days for a total of 1750 mg/m^2 (or 58 mg/kg for patients < 3 years of age). The dose of temozolomide will be rounded up to the nearest 5mg.

5.3.6 **Days -5, -4 and -3: For patients whose corrected creatinine clearance is ≥100 ml/min/1.73m^2:**
Thiotepa 300 mg/m^2/day (10 mg/kg/day for patients < 3 years of age) will be infused intravenously over three hours daily for three days beginning day -5. Carboplatin will be infused intravenously over four hours following the thiotepa daily for three days beginning day -5. The dose of Carboplatin will be calculated using the Calvert formula (AUC=7), surface area (500 mg/m^2) and weight (16.7 mg/kg) and the lowest of the three will be used. A creatinine clearance will be measured prior to **each** dose of Carboplatin. The following is the equation to determine the dose calculated using the Calvert formula.
Patients ≤ 12 years of age:
dose = AUC x [raw creatinine clearance (ml/min) + (body wt.(kg) x 0.36)]
Patients > 12 years of age:
dose=AUC x (raw creatinine clearance (ml/min) + 25)
The maximum dose of carboplatin will be 1050 mg as per the FDA guidelines.
5.3.7 **Days -5, -4 and -3: For patients whose corrected creatinine clearance is ≥ 70 ml/min/1.73m^2 and < 100 ml/min/1.73m^2:**

Thiotepa 200 mg/m^2/day (6.7 mg/kg/day for patients < 3 years of age) will be infused intravenously over three hours daily for three days beginning day -5. Carboplatin will be infused intravenously over four hours following the thiotepa daily for three days beginning day -5. The dose of Carboplatin will be calculated using the Calvert formula (AUC=4.1), surface area (300 mg/m^2) and weight (10mg/kg) and the lowest of the three will be used. A creatinine clearance will be measured prior to **each** dose of Carboplatin. The following is the equation to determine the dose calculated using the Calvert formula.

Patients ≤ 12 years of age:

dose = AUC x [raw creatinine clearance (ml/min) + (body wt.(kg) x 0.36)]

Patients > 12 years of age:

dose=AUC x (raw creatinine clearance (ml/min) + 25)

The maximum dose of carboplatin will be 600 mg as per the FDA guidelines.

5.3.8 **Therapy Scheme:**

Day -10,-9,-8,-7,-6: Temozolomide 175 mg/m^2/dose (or 5.8 mg/kg) orally bid

Day -5,-4,-3: For patients with a creatinine clearance ≥100 ml/min/1.73m^2 Thiotepa intravenously 300 mg/m^2 (or 10 mg/kg) over 3 hours followed by Carboplatin intravenously over 4 hours as calculated by the Calvert formula with AUC=7 or 500 mg/m^2 or 16.7 mg/kg. (maximum dose 1050 mg)

For patients ≥ 70 ml/min/1.73m^2 and < 100 ml/min/1.73m^2

Thiotepa intravenously 200 mg/m^2 (or 6.7 mg/kg) over 3 hours followed by Carboplatin intravenously over 4 hours as calculated by the Calvert formula with AUC=4.1 or 300 mg/m^2 or 10 mg/kg. (maximum dose 600mg)

Day -2: Rest

Day -1: Rest

Day 0: Reinfusion autologous stem cells

Day +1: Filgrastim 5 ug/kg/day daily subcutaneously (or intravenously over four hours). It wil be discontinued when the ANC>1000/mm^3 for three consecutive days or > 10,000/mm^3 for one day.

5.4 Radiation Therapy

Radiation therapy may be given following recovery from the high dose chemotherapy at the discretion of the treating physician. Radiation therapy should start no sooner than 28 days post stem cell reinfusion. Organ toxicity within the radiation field should have resolved. It is highly desirable to start radiation therapy within 42 days after the stem cell reinfusion.

5.5 Continuation therapy with 13-cis-retinoic acid

Patients will begin 13-cis-retinoic acid as early as possible following stem cell reinfusion but not before day 42. One of the principal investigators must be notified if a patient is unable to begin 13-cis-retinoic acid therapy by day 77. **13-cis-retinoic acid should not begin until at least 5 days after the radiation therapy is completed.** 13-cis-retinoic acid may be started if the patient has normal liver (<Grade 2 toxicity) and kidney function, triglycerides < 2x normal, normal calcium, no proteinuria or hematuria. Patients will receive 13-cis-retinoic acid 160 mg/m2/day (5.33 mg/kg/day for patients < 12 kg) orally divided bid for 14 days followed by a 14 day rest for a total of 6 cycles. Round up to the nearest 10mg. Capsules come as 10, 20 and 40 mg sizes. Patients should ingest the capsules whole if at all possible. Children can often be taught to take the capsules by using candy of similar size prior to this phase of therapy. An alternative is to poke a small hole in the capsule and then embed it in a favorite food or soft candy. The hole in the capsule allows it to be "popped" and chewed. If none of the above are successful the capsules can be carefully and totally emptied into a tablespoon of high fat food such as ice cream or peanut butter to administer. Teaching a child to swallow the entire capsule, is feasible and should be encouraged. Under no circumstances should 13-cis-retinoic acid be removed from the capsules for more than 1 hour prior to administering to the patient. 13-cis-retinoic acid must not be put into a solution for administration as this can reduce effective drug levels and can cause increased trans-retinoic acid levels, leading to increased toxicity. If a patient does not meet criteria to start 13-cis-retinoic acid, call the principal investigators for recommendations.

5.5.1 Suggested supportive care during 13-cis-retinoic acid therapy

Topical Vitamin E should be applied to lips BID during 13-cis-retinoic acid therapy if cheilitis develops. All patients should avoid direct sun exposure while on 13-cis-retinoic acid therapy. Tetracycline **is prohibited** during treatment with isotretinoin due to the increased risk of pseudotumor cerebri (benign intracranial hypertension). Vitamin A and vitamin A derivatives should also be avoided during isotretinoin therapy.

5.5.2 Criteria to begin each cycle of 13-cis-retinoic acid

Prior to each cycle, a patient must have:

a. ALT< 5x normal
b. Skin toxicity no greater than grade 1
c. Serum triglycerides < 300 mg/dl
d. Hematuria and proteinuria <1+ on urinalysis. (Trace hematuria and/or proteinuria is allowed)
e. Serum creatinine < 1.5 mg/dl
f. Females of childbearing potential should have a negative pregnancy test and verification of use of contraception.

5.6 Concomitant Medication

5.6.1 Prophylactic antiemetics will be administered at the discretion of the treating physician. The use of dexamethasone for anti-emetic purposes is discouraged because of the concern of inhibiting chemotherapy penetration of the blood brain barrier.

5.6.2 Patients should receive PCP prophylaxis during consolidation and again following stem cell rescue as per institution guidelines.

5.6.3 Tetracyclines and Vitamin A are prohibited during treatment with isotretinoin.

6.0 REQUIRED OBSERVATIONS

6.1 Prior to intensive chemotherapy and autologous stem cell rescue and within 21 days of the start of temozolomide.

6.1.1 Magnetic Resonance Imaging (MRI) scan of head with and without gadolinium.

6.1.2 MRI of the spine with and without gadolinium

6.1.3 Baseline lumbar CSF cytology (by cytospin evaluation) for patients with medulloblastoma, other PNET's, CNS GCT, AT/RT and other tumors when clinically indicated.

6.1.4 Baseline BUN, creatinine,, ≥ 12-hour creatinine clearance or GFR.

6.1.5 Baseline AST, ALT and bilirubin

6.1.6 Baseline electrolytes, calcium, magnesium, and phosphate.

6.1.7 Baseline hemoglobin, platelet count, white cell count and differential.

6.1.8 Serum or urine pregnancy test for pubertal girls

6.1.9 Audiogram

6.1.10 Baseline CSF and serum B-HCG and AFP in patients with CNS germ cell tumors

6.1.11 Other tests needed for good patient care including baseline CXR, echocardiogram, and pulmonary function tests are to be done at the physician's discretion.

6.2 Monitoring During and Following Intensive Chemotherapy

6.2.1 Daily creatinine clearance (at least 8 hour urine collection) following the first and second dose of carboplatin (i.e. prior to the second and third dose of carboplatin).

6.2.2 Bloodwork including complete blood count and chemistries should be done as needed for good patient care.

6.3 Monitoring After Stem Cell Transplant

6.3.1 CSF analysis if positive pre-transplant to assess cell count and differential, protein, and cytology at day 14 following the first dose of 13-cis RA (to coordinate it with CSF 13-cis-RA level), and at 6, 9 and 12 months posttransplant. If CSF cytology is negative pre-myeloablative chemotherapy, post transplant lumbar punctures are required only as clinically indicated. A lumbar puncture at day 14 following the first dose of 13-cis-RA (to coordinate it with CSF 13-cis-RA level) for pharmacokinetic studies is **strongly encouraged but not required.** (See section 6.4.4 for details.)

6.3.2 Head MRI at the start of retinoic acid (approximately 1.5-3 months post transplant), then every 3 months thereafter until 2 years from stem cell infusion; then every 4 months for 1 year, then every 6 months for 1 year and annually thereafter.

6.3.3 MRI of the spine, if initially abnormal, should be repeated at the start of retinoic acid (approximately 1.5-3 months post transplant), then every 3 months thereafter until 2 years from stem cell infusion; then every 4 months for 1 year, then every 6 months for 1 year and annually thereafter. . If the MRI of the spine was initially normal, repeat scans following stem cell transplant should be done at the physician's discretion.

6.3.4 Audiogram is recommended 3 months and one year post transplant; thereafter annually only if abnormal.

6.3.5 Serum BHCG and AFP for CNS germ cell tumors at the start of retinoic acid (approximately 1.5-3 months post transplant), then every 3 months thereafter until 2 years from stem cell infusion; then every 4 months for 1 year, then every 6 months for 1 year and annually thereafter in patients with a history of positive markers.

6.3.6 CSF BHCG and AFP for CNS germ cell tumors at day 14 following the start of 13-cis-retinoic acid (approximately 1.5-3 months post transplant) and then every 3 months post transplant for up to 1 year in patients with positive markers at time of transplantation. If CSF markers are negative pre-myeloablative chemotherapy, repeat lumbar puncture at day 14 of the first cycle of 13-cis-retinoic acid.

6.4 Monitoring During Continuation Therapy with 13-cis-Retinoic Acid

6.4.1 Physical exam prior to each course of 13-cis-retinoic acid.

6.4.2 CBC, electrolytes, BUN, creatinine, calcium, phosphorus, magnesium, triglycerides, ALT, bilirubin, urinalysis and pregnancy test (for women of child bearing potential) prior to each course of 13-cis-retinoic acid.

6.4.3 Pharmacogenetics of 13-cis-retinoic acid. **These studies are strongly encouraged but not required.**

A single 5ml blood sample will be taken from each patient prior to the first course of 13-cis-retinoic acid treatment, and transferred to an EDTA tube and stored at -20^{0}C. DNA obtained from this sample will be genotyped for metabolizing enzymes thought to be involved in the metabolism of 13-cis-RA, such as CYP2C8 and CYP3A7, using PCR techniques established at the Northern Institute for Cancer Research, Newcastle upon Tyne, UK. The sample should be labeled with the patient's unique patient number (assigned at the time of enrollment by the study

operation office at NYU), sample # (see appendix E for numbering samples), PI's name and protocol number which is PBMTC ONC032.

6.4.4 13-cis-retinoic acid pharmacokinetic sampling. **These studies are strongly encouraged but not required.**

Blood and CSF samples will be taken on day 14 of the first course of 13-cis-retinoic acid. 5ml blood samples will be taken and immediately transferred to foil wrapped heparinized tubes at the following time-points: pretreatment and 1,2,4 and 6 hours after oral administration of 13-cis-retinoic acid. Blood samples will be centrifuged at a speed of 2,000 rpm at 4^0C for 5 minutes and the plasma separated, transferred to foil wrapped tubes (size of tube should be such that the plasma nearly fills it, thus preventing oxidation of 13-cis-retinoic acid during storage) and stored protected from the light at -20^0C prior to transportation to Minneapolis. Wherever possible, pharmacokinetic samples should be taken when therapeutic blood samples are obtained. Plasma concentrations of 13-cis-retinoic acid, ATRA and the metabolite 4-oxo-13-cis-retinoic acid, will be determined by HPLC analysis as previously described.[35] Each sample should be labeled with the patient's unique patient number (assigned at the time of enrollment by the study operation office at NYU), sample # (see appendix E for numbering samples), PI's name and protocol number which is PBMTC ONC032.

A single CSF sample (2-5ml) will be obtained at the 2 hour post time point on day 14 of the first course of 13-cis-retinoic acid. The pre-maintenance CSF analysis for malignant cells should be delayed until day 14 of the first course of 13-cis-retinoic acid to coordinate with the CSF pharmacokinetic time point. The CSF sample should be labeled with the patient's unique patient number (assigned at the time of enrollment by the study operation office at NYU), sample # (see appendix E for numbering samples), PI's name and protocol number which is PBMTC ONC032.

See section 6.6 for instructions regarding shipping the CSF and blood samples.

6.5 Table 1: Required Observations and Data Collection First Year of Therapy

Observation	Pre-BMT (within 21 days)	Day –5 ##	Day –4##	6 weeks post-BMT	Day +42-180 (during 13-cis-RA)	3 mos post-BMT	6 mos post-BMT	9 mos post-BMT	1 year post-BMT
Physical Exam	X				X§				X
MRI Head w/wo gadolinium	X			X		X	X	X	X
MRI Spine w/wo gadolinium	X			X**		X**	X**	X**	X**
Lumbar CSF cytology (cell count, cytospin, protein)*	X				X**	X**	X**	X**	X**
CBC with differential and platelets	X				X§	X	X	X	X
Electrolytes, BUN, Cr., Ca, Phos, Mg	X				X§				
AST, ALT, Bilirubin	X				X§				
Triglyceride, urinalysis					X§				
Audiogram	X					X			X
GFR or $\geq$12 hour Creatinine Clearance	X								
$\geq$8 hour Creatinine Clearance		X	X						
Serum/urine pregnancy test^	X				X§				
Serum βHCG/αFP#	X			X**		X**	X**	X**	X**
CSF βHCG/αFP#,**	X			X**		X**	X**	X**	X**
Karnofsky or Lansky score	X								X

*patients with medulloblastoma, PNET, germ cell tumors and when clinically indicated.

** only if positive pre-transplant

^ Pubertal girls

[#] CSN germ cell tumors only

[##] after Carboplatin dose

[$]Prior to each course of cis-retinoic acid

6.6 Table 2: Adjunctive Retinoic Acid Studies.
These studies are strongly encouraged but not required.

Observation	6 weeks post-BMT	Day +42 to 180 (during 13-cis-retinoic acid)
CSF cis-retinoic acid level		X[+]
13-cis-retinoic acid pharmacogenetics/pharmacokinetics	X[@]	X[%] (5 time points)

[@] A single 5ml blood sample will be taken from each patient prior to the first course of 13-cis-retinoic acid treatment, and transferred to an EDTA tube and stored at -20^0C. The sample should be labeled with the patient's unique patient number (assigned at the time of enrollment by the study operation office at NYU), sample # (see appendix E for numbering samples), PI's name and protocol number which is PBMTC ONC032.

[%] On day 14 of the first course of 13-cis-retinoic acid, 5 ml blood samples will be taken and immediately transferred to foil wrapped heparinized tubes at the following time-points: pretreatment and 1, 2, 4 and 6h after oral administration of 13-cis-retinoic acid. Blood samples will be centrifuged at a speed of 2,000 rpm at 4°C for 5 minutes and the plasma separated, transferred to foil wrapped tubes (size of tube should be such that the plasma nearly fills it, thus preventing oxidation of 13-cis-RA during storage) and stored protected from the light at -20°C. Each sample should be labeled with the patient's unique patient number (assigned at the time of enrollment by the study operation office at NYU), sample # (see appendix E for numbering samples), PI's name and protocol number which is PBMTC ONC032.

[+] A single CSF sample (2-5mls) will be obtained on day 14 at the 2hour post oral administration of 13-cis-retinoic acid. CSF samples should be transferred to wrapped tubes nearly filled to the top and stored protected from the light at -20°C. The CSF sample should be labeled with the patient's unique patient number (assigned at the time of enrollment by the study operation office at NYU), sample # (see appendix E for numbering samples), PI's name and protocol number which is PBMTC ONC032.

Execution of an agreement with Children's Hospitals and Clinics of Minnesota for the reimbursement for biological samples (Blood and CSF) is required prior to shipping samples to Children's Hospitals and Clinics of Minnesota, Minneapolis. To verify the status of this agreement between Children's Hospitals and Clinics of Minnesota and your institution, please contact Mary Lamers Tkach (mary.lamers@childrensmn.org) or Lezlie Rabine (lezlie.rabine@childrensmn.org) either via email or phone: 612-813-5913

Please follow the shipping instructions below for shipping sample (Blood and CSF). Payment is contingent upon adherence to these instructions.

- Label the samples with the following format:

PBTMC ONC032
PI's Name
Patient Study #
Sample #

- Batch and send all seven samples in one shipment.
- Include a copy of page 1 of the shipping form (see Appendix E) with the shipment.
- Notify Mary Lamers Tkach (mary.lamers@childrensmn.org) or Lezlie Rabine (lezlie.rabine@childrensmn.org) either via email or phone: 612-813-5913 prior to shipping. Please provide your institution's name, the patient(s) study number(s), and the arrival date. Shipments may only arrive Monday- Friday during regular business hours (8am-5pm).
- Ship samples overnight on 8 pounds of dry ice. Please use FedEx (account #314-971-248) to ship samples to the following address:

Attn:Mary Lamers Tkach or Lezlie Rabine
Children's Hospitals and Clinics of Minnesota
2525 Chicago Avenue S.
CSC-175
Minneapolis, MN 55404

Refer to Appendix E for shipping form. Complete the form and include in shipment to Children's Hospitals and Clinics of Minnesota, Minneapolis.

6.7 Table 3: Required Observations and Data Collection 15 months to 3 years post-BMT

Observation	15 mos post-BMT	18 mos post-BMT	21 mos post-BMT	2 yrs post-BMT	28 months post-BMT	32 months post-BMT	3 yrs post-BMT
MRI Head w/wo gadolinium	X	X	X	X	X	X	X
MRI Spine w/wo gadolinium	X**	X**	X**	X**	X**	X**	X**
Serum HCG/AFP#	X**	X**	X**	X**	X**	X**	X**
Karnofsky or Lansky score				X			X

** only if positive pre-transplant or at the physician's discretion if negative pre-transplant.
# CSN germ cell tumors only

7.0 NEUROPATHOLOGY GUIDELINES/ SPECIMEN SUBMISSION REQUIREMENTS

7.1 The following specimens should be sent from tissue at the time of relapse. However, if no tissue was obtained at relapse or if there is insufficient tissue available, tissue from initial diagnosis is acceptable for submission for central review. The neuropathologist at each participating institution, at the completion of review of each case originating at his/her institution, should submit the following:

- At least one H&E from each block of tumor
- 10 unstained slides from one best block
- Institutional neuropathologists's report

7.2 The slides and report should be sent to:

Sharon Gardner, MD
Steven D. Hassenfeld Children's Center
317 E. 34th Street
New York, NY 10021
Telephone: (212)263-8520 or (212)263-8400
Beeper: (917)812-0526
Email: Sharon.gardner@med.nyu.edu
Fax: (212)263-8410

Please contact Dr. Gardner for the Airborne Express account information prior to sending the pathology samples.

8.0 NEURORADIOLOGY SUBMISSION REQUIREMENTS

8.1 All patients will have central neuroradiological review. Submit the following studies with their corresponding reports to the address below:

- Pre-transplant cranial MRI with and without contrast
- Pre-transplant spinal MRI with contrast
- 1 year post transplant cranial MRI with and without contrast
- 1 year post transplant spinal MRI with contrast, if study was performed
- Cranial MRI at progression (relapse) with and without contrast if relapse occurs less than one year post transplant

- Spinal MRI at progression (relapse) with contrast if relapse occurs less than one year post transplant

8.2 Imaging data may be sent on a CD or by hard copies of films. The imaging data and reports should be sent to:

Sharon Gardner, MD
Steven D. Hassenfeld Children's Center
317 E. 34th Street
New York, NY 10021
Telephone: (212)263-8520 or (212)263-8400
Beeper: (917)812-0526
Email: Sharon.gardner@med.nyu.edu
Fax: (212)263-8410

Please contact Dr. Gardner for the Fedex account information prior to sending the radiology studies.

9.0 EVALUATION OF RESPONSE AND RELAPSE CRITERIA

9.1 Tumor size on enhanced MRI with gadolinium

9.1.1 Continuing Complete Response (CCR): Continuing absence of radiographically identifiable tumor on comparison scans performed at a minimum of 4 weeks apart.

9.1.1 Complete Response (CR): Complete disappearance of all known disease by MRI for a minimum of 4 weeks.

9.1.2 Partial Response (PR): Greater than 50% decrease in tumor size demonstrable by MRI for a minimum of 4 weeks.

9.1.3 Stable Disease (SD): Less than 50% decrease or no reduction in tumor size demonstrable by MRI. Patient fails to qualify for a CR, PR, or PD.

9.1.4 Progressive disease (PD): Disease in previously uninvolved areas without achieving a CR; clinical or radiological evidence of increased volume of > 25% in tumor area with maximum perpendicular diameters in any site of residual disease as compared to immediate pre-study area.

9.1.5 Relapse: Appearance or reappearance of tumor in any site in patients who had responded completely to therapy.

9.2 CSF cytological examination of malignant cells

9.2.1 CR: Complete clearance of all malignant cells on cytospin analysis of lumbar CSF, if previously positive.

9.2.2 No Response (NR): Incomplete clearance of malignant cells on cytospin analysis of lumbar CSF, if previously positive.

9.2.3 Relapse: Presence of malignant cells in the CSF when it was previously clear.

9.3 Evaluation of extracranial metastases

The prolonged latency to resolution of bone CT or MRI abnormalities in response to therapy renders early evaluation of response impossible. It is recommended that consideration be given to biopsying one or more originally abnormal sites on bone scan at three months from marrow reinfusion to evaluate response to therapy.

9.4 Overall rating of tumor responses

In patients with both solid tumor and CSF evaluable for response, a CR will be defined as complete response of both tumor bulk and CSF cells. Progressive disease in either location (tumor bulk or CSF) will define an overall rating of PD.

9.5 Relapse

Relapse is defined as the appearance or reappearance of tumor in any site in patients who had responded completely to therapy.

10.0 DRUG INFORMATION AND TOXICITIES

10.1 **Temozolomide**

10.1.1 Available commercially (Schering Corporation)

10.1.2 Formulation: Temozolomide is supplied as a machine-filled, white opaque, preservative-free, two piece, hard gelatin capsule available in 250 mg, 100 mg, 20 mg, and 5 mg strengths. The 250 mg and 100 mg capsules are larger in size than the 20 mg and 5 mg. Temozolomide capsules are packaged in 30 cc, 28mm 480 Type 1amber glass bottles containing 30 capsules of 5 mg, 20 mg, 100 mg or 250mg strengths.

10.1.3 Storage: Temozolomide capsules should be stored between 2-30° C in amber glass bottles.

10.1.4 Administration: Temozolomide is administered orally on an empty stomach. The drug is approximately 100% bioavailable. The dose should be rounded to the nearest 5 mg. The capsules should not be broken open. However, for young children who cannot tolerate capsules, the capsules may be opened by the parent wearing appropriate protective gloves, and the contents placed into apple sauce or juice, but NOT dairy products. Patients must fast for a minimum of one hour prior to the administration of each dose of temozolomide, and continue fasting for one hour after the administration of each dose. Water is permitted during this period of time, however. Light, non-dairy containing meals, may be eaten within 4 hours prior to each dose (juice, toast, jam). Patients who are obese (greater than 125% above ideal weight for height) will have their doses based on adjusted body weight as described in Appendix A.

10.1.5 Toxicities:

	Common Happens to 21-100 children out of every 100	Occasional Happens to 5-20 children out of every 100	Rare Happens to less than 5 children out of every 100
mmediate: Within 1-2 ays of receiving drug		**Loss of appetite, nausea, vomiting, diarrhea, constipation, headache, rash, itching, increased need to urinate, urinary tract infections**	**Convulsions, dizziness, difficulty walking, confusion, difficulty swallowing, anxiety, partial paralysis or weakness of one side of the body, blood clots which may be life-threatening (L)**
rompt: Within 2-3 eeks, prior to next ourse	**Decrease in the number of red and white blood cells and platelets made in the bone marrow**	**Mouth sores, tiredness, fluid buildup in legs and arms**	**Prolonged decrease in the number of red and white blood cells and platelets made in the bone marrow with an increased risk of infection or death, memory-loss, unable to sleep, depression, muscle aches, blurred or double vision**
elayed: Anytime later uring therapy, excluding		**Hair loss, liver damage**	

ne above conditions			
ate: Anytime after ompletion of therapy			Cancer

10.2 Thiotepa (N,N,N,-Triethylenethiophosphoramide)

10.2.1 Available commercially (Lederle)

10.2.2 Formulation: 15 mg vials in powder form.

10.2.3 Storage: Refrigerate at 2-8°C.

10.2.4 Reconstitution: Reconstitute 15 mg vial in sterile water to give an isotonic solution (since powder contains 80 mg NaCl and 50 mg $NaHCO_3$). A 15 mg vial may be diluted in 15. ml sterile water, and then added to other diluents as needed, e.g., NaCl, dextrose or dextrose-NaCl solutions.

10.2.5 Stability: Reconstituted solutions are stable under refrigeration for five days without loss of potency.

10.2.6 Administration: 300 mg/m^2 (or 10 mg/kg for children < 3 years of age) by intravenous infusion over three hours daily for three days.

10.2.7 Toxicities:

	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, loss of appetite**	**Pain at the injection site, dizziness, headache**	**Hives, skin rash**
Prompt: **Within 2-3 weeks, prior to next course**	**Decrease in the number of red and white blood cells and platelets made in the bone marrow** **At high doses used before marrow transplants: mouth sores, inflammation of the passage between the throat and stomach**	**At high doses used before marrow transplants: inappropriate behavior, confusion, drowsiness, increased liver enzymes in the blood, increased bilirubin in the blood, darkening of the skin**	**Sudden high fever**
Delayed: **Anytime later during therapy, excluding the above conditions**	**Absence of sperm or stopped monthly periods, inability to have children**		
Late: **Anytime after completion of therapy**			

(L) Toxicity may also occur later.

10.3 Carboplatin (1,1-cyclobutane dicarboxylate (2-)-0,0')-platinum)

10.3.1 Available commercially

10.3.2 Formulation: 150 mg prepared as a white lyophilized powder with 150 mg of mannitol in a 20 ml amber vial for injection.

10.3.3 Storage: Intact vials should be stored under refrigeration at 2-8°C.

10.3.4 Reconstitution: 150 mg/vial. When reconstituted with 9.8 ml of sterile water for injection U.S.P., each ml will contain 15 mg carboplatin and 15 mg mannitol at pH 4.6 to 7.0.

10.3.5 Stability: When reconstituted as directed, the solution of carboplatin exhibits no decomposition for at least 24 hours at room temperature. Dilution with saline solution has been associated with increased rates of decomposition. The preparation contains no antibacterial preservatives and should be discarded eight hours after reconstitution.

10.3.6 Administration: AUC=7 or 500 mg/m^2 or 16.7mg/kg (the lowest of the three) by intravenous infusion over four hours.10.3.7Toxicities:

	Common Happens to 21-100 out of every 100 children	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 (L), vomiting (L)**	**Allergic reactions* (possibly severe and life-threatening), rash (L)**	**Metallic taste**
Prompt: **Within 2-3 weeks, prior to next course**	**Low number of white blood cells and platelets (effect on platelets may be greater than on white blood cells)**	**Abnormal levels of certain salts in the body like sodium and potassium (L)**	**Numbness, tingling, clumsiness, damage to the liver (L), damage to the kidney (L), damage to the ear causing hearing and balance problems(L) , hair loss**
Delayed: **Any time later during therapy, excluding the above conditions**			
Late: **Any time after completion of treatment**			**A new leukemia caused by this treatment**

**The incidence of allergic reactions tends to increase after repeated courses of treatment (increased rate of occurrence after six courses noted in adult patients).*
(L) Toxicity may also occur later.

10.4 **Filgrastim**

10.4.1 Available commercially.

10.4.2 Formulation: Available in 300 ug/ml ampules containing 300 ug or 480 ug.

10.4.3 Storage: Store under refrigeration at 2-8°C.

10.4.4 Stability: Any vial left at room temperature for greater than 24 hours should be discarded.

10.4.5 Administration: Administer once daily, subcutaneously without dilution or if necessary dilute with 5% dextrose in water, preferably to concentrations of 15 mcg/ml or greater for IV administration. Dilutions should be prepared as close to the time of administration as possible (up to 24 hours), since the product is preservative-free. When diluting Filgrastim to 5-14 mcg/ml in D5W, it is necessary at all times to add human serum albumin, to reach a final albumin concentration of 2 mg/ml. The dose of Filgrastim is 5 mcg/kg.

10.4.6 Toxicities:

	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 injection site**	**Allergic reaction, low fever**
Prompt: **Within 2-3 weeks, prior to the next course**		**Ache or pain inside the bones, increased levels of liver enzymes and uric acid in the blood, low number of platelets in the blood**	**Enlargement of the spleen, worsening of pre-existing skin rashes, hair loss**
Delayed: **Anytime later during therapy, excluding the above conditions**			**Inflammation of a blood vessel in the skin**
Late: **Anytime after the completion of treatment**			

10.5 Isotretinoin (13 cis-retinoic acid, ACCUTANE, Amnesteem) NSC#329481

10.5.1 Available commercially under the trade name ACCUTANE (Roche Laboratories) and Amnesteem (Bertek Pharmaceuticals) in 10mg, 20mg and 40mg soft gelatin capsules.

10.5.2 Formulation and Stability: The 13-cis isomer of retinoic acid will be used. This is a yellow-orange crystalline powder with a molecular weight of 300.44. Available as an oral gelatin capsule in 10mg, 20mg and 40mg sizes. When the dose is taken in a method other than simply being swallowed, prepare the dose immediately prior to administration due to lack of stability data.

10.5.3 Administration: PO with food or milk to enhance absorption. The following options may be offered to aid in administration of the capsules to children unable or unwilling to swallow the capsules, in order of preference: 1) swallow capsule whole (preferable) OR 2) soften capsule (in warm water) bite and swallow OR 3) soften capsule, bite and suck out contents OR 4) soften capsule, remove contents either with oral syringe (and draw it up) or squish out contents into a small medicine cup and give with fatty food. If at all possible have the child suck on the empty capsule in hopes of getting more of the intended dose.

10.5.4 Toxicities:

	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 and vomiting**	**Anaphylaxis, bronchospasm**
Prompt: **Within 2-3 weeks, prior to the next course**	**Dry skin (L), dry mouth (L), swollen and sore lips (L), photosensitivity, elevated ESR, back pain (L), arthralgia (L), triglyceride elevation (L)**	**Rash (L), eye irritation/soreness (L), joint pains (L), back pain (L), extreme tiredness (L), headache (L), high levels of fat in the blood (L), high levels of liver enzymes in the blood (L), high levels of calcium in the blood, cholesterol elevation (L)**	**Changes in skin color, upset stomach, dizziness, fluid build-up in the brain causing headache and nausea/vomiting and an abnormality of the eyes, low numbers of red and white blood cells, elevated platelet counts, psychiatric disorders including aggressive and/or violent behavior, a condition called retinoic acid syndrome with an increase in white blood cells, fever, difficulty breathing, low blood pressure alopecia, insomnia, appetite disturbances, hyperglycemia, lethargy, malaise, paresthesias, allergic vasculitis (L), chest pain, pancreatitis, hearing impairment, inflammatory bowel disease, visual disturbances, inflammation of the gums, drying of the respiratory tract with voice alteration, respiratory infections**
Delayed: **Any time later during therapy, excluding the above conditions**		**Skeletal hyperostosis**	**Enlarged sections of bones, decrease in the density of bone causing weakened bones, rhabdomyolysis abnormal menses, renal disturbances (WBC in urine, proteinuria, hematuria, renal calculi), calcification of tendon and ligaments**
Late: **Any time after the completion of treatment**	**Birth defects to unborn Children if taken during pregnancy**		

(L) Toxicity may also occur later.

Retinoic acid (RA) may produce birth malformations and should not be administered during pregnancy or to women who may become pregnant while undergoing treatment. There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking RA in any amount. Major human fetal abnormalities related to RA have been documented, including hydrocephalus, microcephalus, abnormalities of the external ear (micropinna, small or absent external auditory canals), microphthalmia, cardiovascular abnormalities, facial dysmorphia, thymus gland abnormalities, parathyroid hormone deficiency, and cerebellar malformation. There also is an increased risk of spontaneous abortion. For female patients of child-bearing age, effective contraception must be used for at least one month before beginning RA therapy, during therapy and for one month following discontinuation of therapy. It is recommended that two reliable forms of contraception be used simultaneously unless abstinence is the chosen method. If pregnancy does occur during treatment, the physician and the patient should discuss the desirability of continuing the pregnancy. All females of childbearing age who will handle the drug to administer to the patient are advised to wear protective gloves.

Isotretinoin must be prescribed under the Committed to Pregnancy Prevention Program (iPLEDGE). Physicians must complete a one-time registration with the manufacturers of Isotretinoin in order to be able to prescribe the drug. Each physician (or their office representative)/pharmacist and patient must be registered on line @ http://www.ipledgeprogram.com (or call 1-866-495-0654 to begin the registration process.)

10.6 Collection and reinfusion of autologous stem cells information and toxicity

10.6.1 General: Leukapheresis (for the collection of peripheral blood stem cells) will be performed using a continuous flow cell separator machine. This machine is commonly used by many blood bank facilities and separates whole blood into some of its components based on the differences in densities.

10.6.2 Toxicities: Adverse reactions similar to those seen with routine blood collection such as lightheadedness, fainting, and vomiting may occur. Also, complications unique to the pheresis procedure including: chills (secondary to extracorporeal cooling of patient blood), volume depletion or overload, hemolysis, blood clotting, bleeding, or air embolism may occur. In addition, in patients weighing less than 40 kg the machine will be primed with irradiated packed red blood cells reconstituted with saline or albumin in order to prevent hypovolemia. Consequently, these patients will be at an increased risk of developing transfusion reactions or blood-borne infections. However, this exposure will be minimal compared with the blood transfusion requirements which these patients will incur following the intensive chemotherapy phase of therapy.

10.6.3 The risks associated with reinfusing the cells include urine discoloration, nausea, vomiting, the odor of the preservative (DMSO) used to store the PBSC, fever, chills, and increased blood pressure. All of these symptoms are temporary and usually resolve after the infusion is complete. As with any experimental procedure, there may be unanticipated side effects.

11.0 MODIFICATION FOR TOXICITY

11.1 Modification during cytoreduction

The creatinine clearance will be determined prior to each dose of carboplatin. If the creatinine clearance drops to < 70 ml/min/1.73m^2, neither the carboplatin nor the thiotepa will be administered.

11.2 Modification during 13-cis-retinoic acid therapy

11.2.1 A dose reduction of 25% (to 120 mg/m^2/day or 4 mg/kg/day if the child weighs < 12kg) for subsequent cycles should be made for the occurrence of any Grade 3 or 4 toxicities EXCLUDING: Grade 3 or 4 hematologic, Grade 3 hepatic, Grade 3 nausea, Grade 3 vomiting, or Grade 3 fever. If the same Grade 3 or 4 toxicity recurs at a 25% dose reduction, then decrease the dose another 20% (to 100 mg/m^2/day or 3.33 mg/kg/day if the child weighs $\leq$ 12kg.) If the same Grade 3 or 4 toxicity recurs after two dose reductions, then discuss with one of the principal investigators before continuing therapy.

11.2.2 It has been reported (rarely) that some patients treated with 13-cis-retinoic acid develop new areas of abnormal uptake on bone scan, likely due to increased bone resorption. If such changes occur during retinoic acid phase in absence of other evidence of tu mor recurrence, discuss with the study chair before reporting as disease progression.

11.2.3 If criteria to begin the next cycle are not met by the date the cycle is due to begin, delay the cycle for one week. If criteria are still not met, hold therapy until criteria are met, and treat at 25% dose reduction (120 mg/m^2/day or 4 mg/kg/day if the child weighs $\leq$12 kg). An additional dose reduction to 100 mg/m^2/day (3.33 mg/kg/day if the child weighs $\leq$ 12kg) should occur if criteria are n ot met within one week after due date for subsequent cycles.

11.2.4 If the serum creatinine increases by > 50% in any cycle of therapy, a creatinine clearance or GFR should be done prior to starting the next cycle, and a urinalysis. If the creatinine clearance and/or GFR are < 50 cc/min/1.73m^2, then call one of the principal investigators for a dose adjustment.

11.2.5 If the patient develops hematuria, proteinuria, and/or hypertension during any cycle of therapy, hold the medication and contact one of the principal investigators.

11.2.6 For localized cheilits, apply topical vitamin E to the lips for subsequent cycles. If this does not control symptoms sufficiently to allow sufficient oral intake, then decrease the dose by 25% to 120 mg/m^2/day or 4 mg/kg/day if the child weighs $\leq$12 kg.

11.2.7 If serum triglycerides are > 300 mg/dl when the next cycle is due, delay starting therapy for two weeks. If it is still > 300 mg/dl, then start the patient on medical therapy for serum triglyceride reduction and begin the cycle at the previous cis-retinoic acid dosage. If the serum triglycerides are < 300 mg/dl by the time the subsequent cycle is due, then continue at the same dosage of cis-retinoic acid. If the triglycerides are still > 300 mg/dl after one cycle on medical therapy, then reduce the cis-retinoic acid dosage by 25% for subsequent cycles.

12.0 SUPPORTIVE CARE GUIDELINES

12.1 During high dose chemotherapy

12.1.1 Protective isolation per local institutional guidelines
12.1.2 All blood products to be irradiated with 1500 cGy before being given to patient
12.1.3 Fungal prophylaxis per institutional guidelines.
12.1.4 For menstruating females recommend: nystatin vaginal suppository 100,000 pv q day. Nortulate 5 mg po q day.
12.1.5 Standard Hickman catheter care per institutional guidelines
12.1.6 Day -10 to day -2 before stem cell reinfusion recommend: trimethoprim (150 mg/m^2/day) and sulfamethoxazole (750 mg/m^2/d); divide into two doses and give q12 hours for PCP. For patient allergic to sulfa drugs, pentamidine may be used.
12.1.7 Prophylaxis against HSV, VZV, and/or CMV will be given in seropositive patients per institutional guidelines.
12.1.8 Documented or suspected infections during the cytopenic phase will be treated with appropriate antibiotics, anti-fungals, and/or antivirals as determined by the treating physician.

12.2 Recommended post transplant instructions

12.2.1 When the ANC $\geq$ 500/uL on 3 repeated determinations, begin trimethoprim (150 mg/m^2/day) and sulfamethoxazole (750 mg/m^2/d); divide into two doses given 2 consecutive days/week until month +12. The trimethoprim/sulfamethoxazole should not be restarted before day +28.

12.2.2 Patients should have immune function evaluation at nine months post stem cell reinfusion to determine when to begin the re-immunization process as per local institutional guidelines.

13.0 STUDY MONITORING-SERIOUS ADVERSE EVENTS

13.1 Adverse events will be graded according to the CTC AE criteria, version 3.0. CTC AE version 3.0 may be downloaded from the CTEP web site (http://ctep.cancer.gov).

13.2 Grade 3 and higher adverse events will be reported to the Protocol Chair and Operations Office within 10 days of the occurrence using the form in Appendix C except as specified in section 13.3.

13.3 Grade 4 and grade 5 adverse events specified in the table require expedited reporting.as detailed below.

Attribution	Grade 4		Grade 5#		Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			AE Report		Report to Study Chair by phone within 24 hours of occurrence and by fax or email using the form in Appendix C within 5 calendar days.
Possible, Probable, Definite	AE Report		AE Report	AE Report	

#: 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(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

13.1 All serious adverse events (defined below), whether or not deemed drug-related or expected, must be reported to the Principal Investigators and the Operations Center within 10 days of occurrence. A serious adverse event is one that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience (the subject was at *immediate* risk of death from the adverse event as it occurred)
-A persistent or significant disability/incapacity
-Progression of disease

In addition, important medical events (see definition below), including hematological, renal, cardiovascular, hepatic,

13.2 Important medical events that may not result in death, be life threatening or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention.

13.3 Serious Adverse Events will be reported in a timely manner to the Data Safety

Monitoring Board and to the study Principle Investigators as per PBMTC guidelines as outlined in Appendix B.

13.4 Participating centers will be notified of unexpected fatal or life-threatening events by the Protocol Chair within 7 calendar days after the Protocol Chair's initial receipt of the information.

14.0 Criteria For Removal From Protocol And Off Study Criteria

14.1 Criteria for removal from protocol

14.1.1 Patient or parental non-compliance or request to withdraw from protocol therapy.

14.1.2 At the discretion of the attending physician (reason must be specified)

14.1.3 Any patient who develops hypersensitivity to temozolomide.

14.2 Removal from protocol follow-up

Patients may be removed from protocol specified follow-up under the following circumstances:
a) Death
b) Parent request
c) Entry onto another protocol therapy

15.0 STATISTICAL CONSIDERATIONS

15.1 Accrual goals will be based solely on the number of patients enrolled with the diagnoses of relapsed medulloblastoma or PNET as we have some historical controls on which to base the analysis. Other diagnoses will be analyzed for survival and toxicity and reported

15.2 For this study, a 2-stage Simon minimax design will be used. For a total of 36 subjects, 17 will be accrued during stage 1 and 19 during stage 2. Given that the "true" response probability is 25%, there is a 76.53% probability of ending the trial during stage 1. A response shall be defined as survival of the patient progression-free for 1-year post-SCT. However, if the "true" response probability is 45% then there is a 5.96% probability that the trial will be stopped in stage 1. The alpha level of the design is 0.04 and the power is 0.8. If 4 or fewer responses are observed during the first stage the trial is stopped early. If after 17 patients are enrolled there are fewer than 5 responders, then further enrollment will be suspended until there are either: 5 documented responders at which time accrual will be re-initiated or 13 documented non-responders at which time the study will be closed. If 13 or fewer responses are observed by the end of the trial, then no further investigation of the drug combination is warranted. Given a "bad" response rate of 25%, the expected sample size for the trial is 25.1.

15.3 Although 1-year progression-free survival should approximate longer survival based on historical controls, 3-year progression-free survival will be estimated using the method of Kaplan and Meier.

15.4 Stopping Rules

The study will be stopped if 3 of the first 9 or 4 of the first 20 patients enrolled (regardless of diagnosis) die from transplant-related toxicity OR if after 20 patients are enrolled the toxic mortality rate is >20%. Deaths from progressive disease do not apply to stopping rules.

16.0 Gender and Ethnic Origin

There is no compelling evidence to suggest that outcome of treatment for recurrent brain tumors is dependent on gender or ethnicity. Hence, the study size will not be adjusted to ensure high power to detect differences in outcome in groups defined by ethnicity or gender.

17.0 CONSENT PROCEDURES

The investigational nature and objectives of this trial, the procedures and treatments involved and their attendant risks, discomforts and benefits, and potential alternative therapies will be carefully explained to the patient or the patient's parents/legal guardians (if he/she is a child), and a signed informed consent document will be obtained. Where deemed appropriate by the treating physician and the child's parents/legal guardians, the child will also be included in all discussions about the trial and verbal assent to participate will be obtained.

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Appendix A:

Method of Calculating Adjusted Body Weight

IBW= ideal body weight

Patients over 18 years of age

Male IBW = 50 kg + 2.3 kg x number of inches over 5 feet

Female IBW = 45.5 kg + 2.3 kg x number of inches over 5 feet

Patients 1-18 years of age

a) Less than 60 inches

IBW = $(ht^2 \times 1.65)/1000$ where ht = cm, IBW = kg

b) Greater than or equal to 60 inches

Males IBW = 39 kg + 2.27 kg x number of inches over 5 feet

Female IBW = 42.2 kg + 2.27 kg x number of inches over 5 feet

To calculate adjusted body weight:

1) Actual body weight – IBW = Excess weight
2) Excess weight x 40% = weight adjustment
3) Adjusted body weight = IBW + weight adjustment

Appendix B: Guidelines for Reporting Adverse Events

It is recognized that high-dose chemotherapy with stem cell or bone marrow rescue is associated with significant toxicities that are an anticipated consequence of therapy rather than an adverse event. Except where otherwise specified, the NCI/DCT Common Toxicity Criteria version 3.0 (http://ctep.cancer.gov/reporting/ctc.html) will be used to grade adverse events, utilizing the bone marrow transplant-specific adverse event grading criteria.

Complex/multicomponent adverse events will be graded using the appropriate adverse event reporting scale (see CTC Appendix 6 – BMT Complex/Multicomponent Events). Reporting adverse events will be in addition to reporting of study toxicities as part of study data reporting requirements.
Adverse events will be reported to the Protocol Chair and to the PBMTC Operations Center. Events will be reported using the PBMTC "SERIOUS ADVERSE EVENT ASSESSMENT FOR PATIENTS ENROLLED ON PBMTC TRIALS" form (Appendix C). Events will be classified using the following criteria:

Hematologic Toxicity
The following modified criteria will be used to grade specified hematologic toxicities.
Neutrophils:
Grade 3: Neutrophils ≥100 but <500/ul for duration of 4 to 8 weeks.
Grade 4: Neutrophils <100 for > 4 weeks or <500/ul for duration >8 weeks.
Grade 5: Death due to infection associated with neutrophils <500/ul.
Grade 3 and higher neutrophil toxicities will be reported to the Protocol Chair and Operations Center as specified in section 13.0.
Platelets:
Grade 3: Platelets ≥10,000 but <20,000/ul on day 100, independent of transfusions for 7 days, without other contributing causes.
Grade 4: Platelets <10,000/ul on day 100, independent of transfusions for 7 days, without other contributing causes.
Grade 5: Death due to hemorrhage associated with platelets <20,000/ul.
Grade 3 and higher toxicities will be reported to the Protocol Chair and Operations Center as specified in section 13.0.

Transfusions:
Blood transfusions will be reported when Grade 3 or higher according to CTC BMT guidelines as specified in section 13.0.

Non-Hematologic Toxicity
Unless otherwise noted, non-hematologic toxicities will be graded by the Common Toxicity Criteria version 3.0.
The following non-hematologic Adverse Events will be reported to the Protocol Chair and Operations Center as specified in section 13.0.

Cardiovascular: Grade 3 or higher using the standard CTC scale
Grade 2 or higher vascular leak syndromes.
Coagulation: Grade 3 or higher (thrombotic microangiopathy)
Dermatology: Grade 3 or higher (rash/desquamation)
Anaphylactic reactions: All to be reported as serious adverse events regardless of cause.
Endocrine: Grade 3 or higher using the standard CTC scale.
Gastrointestinal: Vomiting: Grade 4 or higher using the standard CTC scale.
Diarrhea associated with graft versus host disease. Grade 3 or higher using the CTC scale for BMT studies.
Mucositis/stomatitis: Grade 3 or higher using the CTC scale for stomatitis/pharyngitis/mucositis for BMT studies.
TPN administered for mucositis will not be reported.
Hepatic: Bilirubin: Grade 3 or higher using the CTC scale for GVHD.

SGOT/SGPT: Grade 3 or higher using the standard CTC scale, and only if not associated with GVHD or VOD (otherwise it will be reported according to the criteria for the appropriate multicomponent event).
VOD: Grade 3 or higher using the CTC scale for complex/ multicomponent events. Lifethreatening (Grade 4) VOD will be defined as weight gain >10%, creatinine >2, and O2 dependent. If 2 out of 3 factors present, it will be considered severe. Weight gain will not be reported separate from VOD.
Infection: Only infections requiring hospitalization, documented invasive fungal infections requiring intravenous therapy and any episodes of septic shock will be reported.
Metabolic/Laboratory: Grade 4 using the standard CTC scale.
Neurologic: Grade 3 or higher using the standard CTC scale.
Pulmonary: Grade 3 or higher using the standard CTC scale, except Grade 2 FEV1 and pneumothorax will be reported. Abnormalities in DLCO will not be reported separately but will be reported according to the associated level of pulmonary dysfunction.
Renal: Grade 3 or higher using the standard CTC scale, and only if not associated with GVHD or VOD (otherwise it will be reported according to the criteria for the appropriate multicomponent event).
Grade 3 or greater proteinuria and renal failure will be reported.
Genitourinary: Cystitis/hematuria: Grade 3 or higher using the standard CTC scale.
Bladder irrigation will be reported as Grade 3.
Other required treatment modalities will be reported as grade 4.
Pregnancy: If a female patient (or the sexual partner(s) of a male patient) becomes pregnant while receiving protocol therapy, the Protocol Chair and Operations Center should be notified immediately.
GVHD: Only the first incident of Grade 3 or greater GVHD at any site will be reported.

OTHER ADVERSE EVENTS
All other adverse events will be reported according to the following criteria:
Patients will be followed for treatment-related toxicity for 100 days. After 100 days patients will not be followed for treatment-related toxicity except for death, the first episode of extensive chronic GVHD, relapse, or any other event, which is felt likely, probably, or definitely due to the study treatment. Events in these categories will continue to be reported until the study closes to further follow-up. Patient events that do not meet the above criteria (e.g., hyperglycemia from steroid therapy) will not be reported to the IRB after 100 days as they are common in the population of bone marrow transplant recipients, but unlikely to be directly related to the study treatment.
In addition to reporting events to the Protocol Chair and the PBMTC Operations Center, adverse events also will be reported to institutional review boards. Adverse events, grades 1-2, specified in the consent as occasional (happens to between 5-20% of patients) or common (happens to more than 20% of patients) will not be reported to the IRB.
Adverse events, grade 3 or 4 will be reported to the institutional IRB using the criteria set forth in the above modified BMT toxicity scale.

Appendix C: PEDIATRIC BLOOD AND MARROW TRANSPLANT CONSORTIUM ADVERSE EVENT ASSESSMENT FOR PATIENTS ENROLLED ON PBMTC TRIALS

PLEASE SUBMIT THIS FORM AS SPECIFIED IN THE STUDY PROTOCOL

Protocol Title: _____

1. Patient Information			
Patient identifier:	**Age:** **Date of Birth:**	**Sex:**	**Weight:**

2. Adverse Event Assessment	
Date of Event: **Outcome Attributed to Adverse Event** (blacken all that apply	**Date of Report:** ☐ **death** ☐ **life-threatening** ☐ **hospitalization-initial or prolonged** ☐ **disability** ☐ **congenital anomaly** ☐ **required intervention to prevent permanent** ☐ **impairment/damage** ☐ **other**
Type of Event ☐ **Expected** ☐ **Unexpected**	
Description of Event: **Action Taken:** **Protocol Treatment At Time of Event:** **Dose Level (if applicable):**	
Relevant Tests/Lab Data, include dates:	
Other Relevant History, including pre-existing medical conditions and concomitant medications:	
Probable or presumed cause of event:	
Relationship to study agent:	☐ **Definite** ☐ **Probably** ☐ **Possible** ☐ **Not related** ☐ **N/A**
Has this Event Been Reported to your institution's IRB?	☐ **Yes** ☐ **No**

Investigator: _____ **Date:** _____

Institution: _____

Protocol Chair Review:

Action to be taken:

_____ None, continue protocol approval

_____ Protocol suspended pending additional review

_____ Protocol closed

_____ _____
Signature of Protocol Chair Date

Please forward copy of this form to Operations Center, Fax (816)855-1700 within 7 days of receipt.

Protocol Monitor Review

Assessment Review:

_____ Agree with Protocol Chair's assessment. No further action required.

_____ Disagree with Protocol Chair's assessment. Further action required. (If further action is required, please detail below.)

_____ _____
Signature of Protocol Monitor Date

_____ _____
Signature of Protocol Monitor Date

Please forward copy of this form to Operations Center, Fax (816)855-1700 within 5 days of receipt.

Appendix D

INFORMED CONSENT TO PARTICIPATE IN RESEARCH

High dose Temozolomide, Thiotepa and Carboplatin with Autologous Stem Cell Rescue Followed by Continuation Therapy with 13-Cis-retinoic Acid in Patients with Recurrent/Refractory Malignant Brain Tumors

ONC032P

This is a clinical trial (a type of research study involving human patients). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

You are being asked to take part in this study because you have a brain tumor that has not responded to treatment or has come back after treatment. This is called a recurrent brain tumor.

This research is part of a nation-wide study coordinated by the Pediatric Blood and Marrow Transplant Consortium.

WHY IS THIS STUDY BEING DONE?

The current standard treatment for children with recurrent brain tumors has been standard dose chemotherapy. The tumor responds by shrinking, but returns again in months.

Researchers have used high doses of combination chemotherapy followed by a stem cell rescue to treat recurrent brain tumors with moderate success. Stem cells are cells in the bone marrow that produce blood cells. The stem cells are collected from the blood of the patient before the high dose chemotherapy. Patients are given high doses of chemotherapy to kill every brain tumor cell, but in the process the cells of the bone marrow are also killed. The previously collected stem cells are then infused into the patient to rescue the bone marrow and allow for healthy blood cells to re-populate and grow in the bone marrow. Initial studies used the drug etoposide along with carboplatin and thiotepa for the high dose chemotherapy. Patients had severe side effects, especially severe mouth-sores, thought mainly due to the etoposide, and some patients died from these side effects.

Recent studies have shown that a new drug, temozolomide, is active against some types of brain tumors. When it was given as a single drug to children with solid tumors, the side effects were considered to be tolerable. Temozolomide is given by mouth. In this study, researchers want to give high dose chemotherapy that includes the drugs temozolomide in place of etoposide, along with thiotepa and carboplatin. Patients will then be given their own stem cells back to rescue the bone marrow from the chemotherapy. A preliminary trial using this new drug combination was performed and has shown that patients tolerate this drug combination, even at the very high doses that will be used in this protocol.

Another drug that is being used in pediatric cancer treatment is called 13-cis-retinoic acid. This drug is closely related to vitamin A. It is taken by mouth. Cancer cells are immature cells that have not "grown up" into adult cells that do work in the body. 13-cis-retinoic acid is thought to act on some types of cancer cells to make them mature into cells that function in the body. It has also been shown in the laboratory to cause some brain tumor cells to undergo apoptosis. It has been used in other types of pediatric cancers and research is just beginning using it for treatment of recurrent brain tumors. In this study researchers want to give patients 13-cis-retinoic acid for 6 months after they recover from the high dose chemotherapy with stem cell rescue.

In summary, the purpose of this study is to:

- Find out what effects (good and/or bad) treatment with high dose temozolomide, thiotepa and carboplatin with a stem cell rescue followed by 13-cisretinoic acid has on children and adolescents with recurrent/refractory brain tumors

- Find out how the body uses 13-cisretinoic acid by studying the patient's blood levels and proteins in the blood that break down the 13-cisretinoic acid
- Determine how well 13-cisretinoic acid penetrates into the spinal fluid.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

It is expected that 75 patients will take part in this study, nationwide, and "X" patients will be enrolled at this institution.

WHAT IS INVOLVED IN THE STUDY?

Before starting study treatment, you will have received chemotherapy to decrease the size of the tumor. You and your physician will have decided this treatment before entering this study. During this chemotherapy, you will have your stem cells collected. After collection, the stem cells are frozen and stored until they are needed after the high dose chemotherapy. A separate consent will be obtained for the collection of stem cells. The stem cell collection is not part of this study.

High Dose Chemotherapy – Temozolomide, Thiotepa, and Carboplatin
The high dose chemotherapy given during this phase is myeloablative. This means that it destroys the bone marrow. If the stem cells were not given to rescue the bone marrow, new blood cells would not be able to develop in the body.

Various methods will be used to give the drugs to you. Some drugs will be given by capsule, tablet or liquid through the mouth (PO). Other drugs will be given using a needle inserted into a vein (IV). Still other drugs will be given with a needle inserted directly under the skin (SC).

The chemotherapy is scheduled as a "countdown" to day 0. On day 0 the stem cells are given back to you. The chemotherapy regimen for this study is as follows:

Day:	Temozolomide	Thiotepa	Carboplatin
Day 10	X		
Day 9	X		
Day 8	X		
Day 7	X		
Day 6	X		
Day 5		X	X
Day 4		X	X
Day 3		X	X
Day 2	Rest		
Day 1	Rest		
Day 0	Peripheral Blood Stem Cell/Bone Marrow Infusion		

- Temozolomide is given PO twice a day
- Thiotepa is given by IV over 3 hours
- Carboplatin is given by IV infusion over 4 hours immediately after the thiotepa
- Filgrastim (G-CSF) is a drug to stimulate the production of white blood cells. It will be given IV or SC starting on the day after the stem cell infusion and continue until enough white blood cells are present in the blood to fight infection. Usually this will require 2 weeks of G-CSF treatment.

Continuation Therapy - 13-Cis-retinoic acid
This phase of treatment will begin about 6 to 10 weeks after the stem cell rescue. You will receive the 13-cis-retinoic acid by mouth twice a day. It is given for 14 days followed by a 14 day rest period. This cycle is given 6 times for a total of 6 months of treatment.

You will be given a "road map" which is a calendar of treatment. It will tell you what days of the cycle the specific chemotherapy drugs are given.

Standard tests and procedures
The following tests and procedures are part of regular cancer care and may be done even if you do not join the study.

- History and physical examination
- Frequent Blood Counts
- Frequent labs to monitor blood chemistry
- Tests to monitor hearing
- Tests to monitor heart functioning
- Urine tests to monitor kidney functioning
- Spinal taps may be done to check for tumor cells in the spinal fluid and monitor for tumor growth
- X-ray, CT, and MRI scans to evaluate response to treatment
- Pregnancy test for all females of childbearing age before chemotherapy is given
- Bone marrow aspirate/biopsy
- Transfusions with red cells and platelets. Red blood cell transfusions are given so that you do not develop anemia. Anemia occurs when there are not enough red blood cells produced to carry oxygen to the body's cells. You may also receive platelet transfusions. Platelets are blood cells that help your blood clot.

Research study tests and procedures
The following tests will be done because you are part of this study. These tests are not part of standard care.

Researchers want to study how your body breaks down and uses the 13-cis-retinoic acid. This is done by measuring levels of the drug in blood samples and by studying enzymes (proteins in the body) that break down the drug.

This is an optional part of the study. At the end of the consent, there is are check boxes for you to check YES if you want to take part, or NO if you do not.

If you choose to participate, 1 teaspoon of blood (5 ml) will be drawn from your central line at the following times during the first cycle of 13-cis-retinoic acid:

- Before the first dose of 13-cis-retinoic acid
- On the 14th day of 13-cis-retinoic acid, before that day's dose, and 1, 2, 4 and 6 hours after that dose.

Some patients will have spinal taps during their treatment to monitor for tumor growth and tumor cells. For these patients we would like to collect extra spinal fluid during one routine spinal tap to measure 13-cis-retinoic acid in the spinal fluid. The spinal tap would be done on the 14th day of first cycle of 13-cis-retinoic acid, two hours after the morning dose of 13-cis-retinoic acid. The purpose of this aspect of the study is to determine the level of 13-cis-retinoic acid that penetrates into the spinal fluid.

HOW LONG WILL I BE IN THE STUDY?

You will be treated on this study for about 7 to 8 months. We would like to continue to examine you by performing follow-up tests that may include medical histories, physical exams, blood tests, CT/MRI scans, and spinal taps. We would also like to continue to collect some information about how you are doing for as long as you will allow.

Your doctor may decide to take you off this study if you do not respond to the treatment or if the side effects are too severe. You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk with your doctor. If you receive high dose chemotherapy and decide to stop participation in this study without receiving a stem cell transplant, there is a potential risk that your bone marrow may not

continue to produce the needed amount of blood cells. This would result in a condition called aplastic anemia. Aplastic anemia can be life threatening.

Even if you receive a stem cell transplant and your bone marrow continues to produce the needed amount of blood cells, you may still develop an infection. Therefore, it is recommended that you remain under medical care until your immune system recovers from therapy, even if you are no longer participating in this study.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for side effects. You should discuss them with your doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and less uncomfortable. Many side effects go away shortly after the chemotherapy drugs are stopped, but in some cases side effects can be serious or life-threatening or long lasting or permanent.

Some chemotherapy drugs can damage the blood-producing cells in the bone marrow. This results in periodic low blood counts in between treatments, which can increase risk for serious infection, bleeding or anemia. Some chemotherapy can cause nausea and vomiting. Medications can be given to help prevent this. Some chemotherapy can affect the heart, lungs, kidneys, liver and/or hearing. Tests will be done to monitor the function of these organ systems.

Risks and possible side effects related to the chemotherapy we are studying include the following:

Carboplatin

	Common Happens to 21-100 out of every 100 children	**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 (L), vomiting (L)	Allergic reactions*(possibly severe and life-threatening), rash (L)	Metallic taste
Prompt: Within 2-3 weeks, prior to next course	Low number of white blood cells and platelets (effect on platelets may be greater than on white blood cells)	Abnormal levels of certain salts in the body like sodium and potassium (L)	Numbness, tingling, clumsiness, damage to the liver (L), damage to the kidney (L), damage to the ear causing hearing and balance problems (L), hair loss
Late: Any time after completion of treatment			A new leukemia caused by this treatment

**The incidence of allergic reactions tends to increase after repeated courses of treatment (increased rate of occurrence after six courses noted in adult patients).*
(L) Toxicity may also occur later.

13-cis-retinoic acid:

	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 and vomiting	Anaphylaxis, bronchospasm

Prompt: Within 2-3 weeks, prior to the next course	Dry skin (L), dry mouth (L), swollen and sore lips (L), photosensitivity, elevated ESR, back pain (L), arthralgia (L), triglyceride elevation (L)	Rash (L), eye irritation/soreness (L), joint pains (L), back pain (L), extreme tiredness (L), headache (L), high levels of fat in the blood (L), high levels of liver enzymes in the blood (L), high levels of calcium in the blood, cholesterol elevation (L)	Changes in skin color, upset stomach, dizziness, fluid build-up in the brain causing headache and nausea/vomiting and an abnormality of the eyes, low numbers of red and white blood cells, elevated platelet counts, psychiatric disorders including aggressive and/or violent behavior, a condition called retinoic acid syndrome with an increase in white blood cells, fever, difficulty breathing, low blood pressure, alopecia, insomnia, appetite disturbances, hyperglycemia, lethargy, malaise, paresthesias, allergic vasculitis (L), chest pain, pancreatitis, hearing impairment, inflammatory bowel disease, visual disturbances, inflammation of the gums, drying of the respiratory tract with voice alteration, respiratory infections
Delayed: Any time later during therapy, excluding the above conditions		Skeletal hyperostosis	Enlarged sections of bones, decrease in the density of bone causing weakened bones, rhabdomyolysis abnormal menses, renal disturbances (WBC in urine, proteinuria, hematuria, renal calculi), calcification of tendon and ligaments
Late: Anytime after the completion of treatment	Birth defects to unborn children if taken during pregnancy		

(L) Toxicity may also occur later.

A note to mothers: 13-cis-retinoic acid causes severe birth defects. If you are pregnant or there is any chance you might become pregnant, you must not ingest this drug (allow any of it to get on food or get in your mouth). If you handle the liquid from the capsules, you must wash your hands immediately afterwards or wear gloves.

Tetracycline must not be taken during treatment with 13-cis-retinoic acid due to the increased risk of pseudotumor cerebri (benign intracranial hypertension). Vitamin A and vitamin A derivatives should also be avoided during isotretinoin therapy.

Temozolomide:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to less than 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Loss of appetite, nausea, vomiting, diarrhea, constipation, headache, rash, itching, increased need to urinate, urinary tract infections	Convulsions, dizziness, difficulty walking, confusion, difficulty swallowing, anxiety, partial paralysis or weakness of one side of the body, blood clots which may be life-threatening (L)
Prompt: Within 2-3 weeks, prior to next course	Decrease in the number of red and white blood cells and platelets made in the bone marrow	Mouth sores, tiredness, fluid buildup in legs and arms	Memory-loss, unable to sleep, depression, muscle aches, blurred or double vision
Delayed: Anytime later during therapy, excluding the above conditions		Hair loss, liver damage	
Late: Anytime after completion of therapy			Cancer

Thiotepa:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to less than 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, loss of appetite	Pain at the inject site, dizziness, headache	Hives, skin rash
Prompt: Within 2-3 weeks, prior to next course	Decrease the number of red and white blood cells and platelets made in the bone marrow At high doses used before marrow transplants: mouth sores, inflammation of the passage between the throat and stomach		
Delayed: Anytime later during therapy, excluding the above conditions	Absence of sperm or stopped monthly periods, inability to have children		

(L) Toxicity may also occur later.

G-CSF:

	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 injection site	Allergic reaction, low fever
Prompt: Within 2-3 weeks, prior to the next course		Ache or pain inside the bones, increased levels of liver enzymes and uric acid in the blood, low number of platelets in the blood	Enlargement of the spleen, worsening of pre-existing skin rashes, hair loss
Delayed: Anytime later during therapy, excluding the above conditions			Inflammation of a blood vessel in the skin
Late: Anytime after the completion of treatment			

Reproductive risks: Because the drugs and/or radiation therapy in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. Ask about counseling and more information about preventing pregnancy. The administration of chemotherapy and radiation described may cause infertility (being less able to produce a viable egg or sperm). We will talk to males who have reached puberty about sperm banking.

During and after the infusion of the stem cells, you may experience breathing difficulties due to clumps of stem cells and/or fat that become trapped in the lungs, In addition, contamination of the stem cells with bacteria and introduction of infection might occur.

While your doctors and nurses are very experienced at treating these problems, it is possible, though unlikely that you could die from an infection, bleeding or another complication. It is also possible that your bone marrow may not recover after your stem cells are given back to you. In the event that the bone marrow does not recover, additional stem cells will be given , if available.

For more information about risks and side effects, ask your doctor and read your chemotherapy drug sheets that are attached to this consent.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:
- Standard chemotherapy
- No therapy at this time with care to help you feel more comfortable
- Radiation therapy if you have not already received the maximum dose
- High dose chemotherapy with autologous stem cell rescue using another high dose chemotherapy regimen.

Please talk to your doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

Pediatric Blood and Marrow Transplant Consortium
Food and Drug Administration
National Cancer Institute
Children's Hospitals and Clinics Institutional Review Board
New York University Hospital Institutional Review Board

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not waiving any rights that you might otherwise have.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the Principle Investigator at your Institution.

If you have any questions about your rights as a research participant or any complaints that you feel you cannot discuss with the investigators, you may call the Director of your Institutional Review Board.

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's *Cancer Information Service* at
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the *NCI's Web site* at http://www.nci.nih.gov/cancerinfo/

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

SIGNATURE

I agree to take part in this study.

Please answer the following questions by checking YES or NO and entering your initials

#1: I give my consent for the collection of blood for the 13-cisretinoic acid studies.

#1: □ YES □ NO _____
initials

#2: I give my consent for the collection of extra spinal fluid for the 13-cisretinoic acid studies.

#2: □ YES □ NO □ Doesn't apply/Not having spinal taps _____
initials

Participant_____Date _____

Patients 18 years of age or older are required to sign. Patients less than 18 may choose to sign or this may be left blank.

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP_____Date _____

IRB# IRB Approved:

Appendix E: PBMTC ONC-032: Collection and Shipment of Biological Samples

☐ **The study participant consented to biological portion of PBMTC ONC-032P**

Patient Study Number:	
Date Consented:	
Institution:	
PI at the Institution:	

Please complete the following form and send with samples to Children's Hospitals and Clinics of Minnesota, Minneapolis (for address and contact information see shipping instructions).

Administration of 13-cis-RA:

Weight ____ S.A. ____ *GFR/ Creatinine clearance ____ *Date of GFR/Creatinine clearance ____

13-cis-RA dose (mg) ____ Time of administration ____ *Document most current measurement prior to 13-cis-RA administration

Capsules swallowed with milk ____ **OR** Capsules snipped / mixed with ice-cream ____

Other (please specify) ____

Study day ____ (enter if not Day 14 of treatment) Treatment course 1, 2, 3, 4, 5, 6 (circle answer)

Please collect the following samples according to the instructions listed below:

Timing	Sample #	Timing	Sample	Amount	Time/Date Taken	Time Due
Prior to first course of 13-cis-retinoic acid treatment	1	6 weeks post BMT (prior to first course of 13-cis-retinoic acid)	Blood (in EDTA tube -20^{0}C prior to shipping)	5ml		
Day 14 of first course of 13-cis-retinoic acid treatment (Day +42 to 180 post-BMT)	2	Pre-oral administration of 13-cis-retinoic acid	Blood	5 ml		
	3	1 hour post treatment	Blood	5ml		
	4	2 hours post treatment	Blood	5ml		
	5	**2 hours post treatment**	**CSF**	**2-5 ml**		
	6	4 hours post treatment	Blood	5 ml		
	7	6 hours post treatment	Blood	5 ml		

Day 14 Blood Preparation:

- Samples should, wherever possible, be collected when therapeutic blood samples are obtained
- Collect samples in heparinized tubes wrapped with aluminum foil.
- Centrifuge each blood sample at 2,000-3,000rpm at 4°C for 5 minutes in the dark in order to separate plasma.
- Transfer plasma to foil wrapped tube (ideally such that plasma sample fills the tube) and freeze at -20^{0}C prior to transport.

Day 14 CSF Preparation:

- **Transfer CSF to a foil wrapped tube and store at -20^{0}C prior to transport.**

Shipping samples to Children's Hospitals and Clinics of Minnesota, Minneapolis:

Once samples have been received, reimbursement will be processed. Reimbursement is contingent on the following instructions:

- Label the samples with the following format:
  PBTMC ONC032
  PI's Name
  Patient Study #
  Sample #
- Batch and send all seven samples in one shipment.
- Include a copy of the shipping form (previous page) with the shipment.
- Notify Mary Lamers Tkach (mary.lamers@childrensmn.org) or Lezlie Rabine (lezlie.rabine@childrensmn.org) either via email or phone: 612-813-5913 at least 24 hours prior to shipping. Please provide your institution's name, the patient(s) study number(s), and the arrival date. Shipments may only arrive Monday- Friday during regular business hours (8am-5pm).
  - Ship samples overnight on 8 pounds of dry ice. Please use FedEx (account #314-971-248) to ship samples to the following address:

Attn:Mary Lamers Tkach or Lezlie Rabine
Children's Hospitals and Clinics of Minnesota
2525 Chicago Avenue S.
CSC-175
Minneapolis, MN 55404