A STUDY OF THE CHILDREN'S NEURO-ONCOLOGY CONSORTIUM

FEASIBILITY OF USING CONCURRENT CARBOPLATIN AND REDUCED DOSE CRANIOSPINAL RADIATION (24 GY) FOR METASTATIC MEDULLOBLASTOMA AND HIGH-RISK SUPRATENTORIAL PNET AND METASTATIC PNET

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1.0 GOALS AND OBJECTIVES

To study the efficacy of the combination of reduced dose craniospinal radiation (reduced from standard of care dosing at 36 Gy to 24 Gy) with concurrent carboplatin and vincristine administration for metastatic classical histology medulloblastomas and high-risk supratentorial PNETs and metastatic PNETs.

2.0 OVERVIEW AND STUDY DESIGN

This study is to look at the efficacy of reducing the dose of craniospinal radiation to limit adverse effects, while adding concurrent carboplatin administration during radiation with weekly vincristine for metastatic medulloblastomas and high-risk supratentorial PNETs and metastatic PNETs. Pilot data from Children's Oncology Group (COG) study 99701 show excellent results with daily carboplatin infusion during radiation for high risk central nervous system tumors (Jakacki et al, 2006). This study had an 89% 3 year event free survival for classical histology metastatic medulloblastoma. Anaplastic medulloblastomas did poorly and will be excluded from the current study.

Although the COG 99701 study had excellent event free survival, 36 Gy radiation dose to the craniospinal axis was used. This dosage is known to be associated with extremely poor quality of life as an adult (Ribi et al, 2005, Packer et al, 1994). The improvement of survival of COG 99701 over all prior studies appears to be due to the addition of carboplatin during radiation. The current study proposes to see if the addition of carboplatin during radiation allows for lowering the craniospinal radiation dose to 23.4 Gy, a dose which is known to be associated with a satisfactory quality of life for adult survivors (Ribi et al, 2005, Packer et al, 1994).

In order to assess efficacy we would accept equivalency in terms of 90% event free survival from progression at 3 years. We will re-assess the therapy after every 10 patients completes the study. One

failure within every ten patients would close the study. Following concurrent carboplatin, vincristine, and craniospinal radiation at 24 Gy, patients will receive the current standard adjuvant chemotherapy.

3.0 BACKGROUND AND RATIONALE

PNET is a class of brain tumors that consists of medulloblastomas (in the cerebellum) and supratentorial PNETs. These are two subgroups of the same tumor type that have the same risk profile. They tend to metastasize through the cerebral spinal fluid pathways. PNETs are classified by the World Health Organization as grade IV tumors (highly malignant) (Kleihues & Cavenee, 2000). PNETs occur most commonly in children aged 4 weeks to 10 years, with peak age of diagnosis at age five. Up to one third of patients have metastatic disease at diagnosis (Kleihues & Cavenee, 2000). Disseminated disease has been found to be an adverse prognostic factor (Packer et al, 1994; Boyett et al, 1995). Other poor prognostic factors include primary tumors that are not cerebellar or pineal; age less than 3 years; and significant post-operative residual tumor (Cohen et al, 1995; Jenkin et al, 1990).

Adding chemotherapy to radiation is proposed to enhance the response on tumor burden (Steel, 1979). This increased response may occur because of increased cell death, decrease in radiation-induced damage repair, and prevention of tumor cell rebound growth in response to radiation therapy (Wilkins et al, 1993). Cells may also be induced out of the resting phase and become more chemo and radio-sensitive. It is also postulated to eliminate systemic micrometastases concurrently to the primary tumor.

It is known that platinums can potentiate the efficacy of radiation (Douple & Richmond, 1978). Platinums radiosenstize hypoxic cells and possibly keep tumor cells in the radiosensitive phase of the cell cycle (Skov & MacPhail, 1991; Douple et al, 1985). Inhibition of "sublethal damage repair" and "potentially lethal damage recovery" is caused by the potentiation of radiation biochemically (Fu &

Phillips, 1991). This has been demonstrated by cisplatin in a brain tumor cell line (Wilkins et al, 1993). In addition, chromosomal aberrations may be increased (Schwachoffer et al, 1991).

Frequent low-dose carboplatin administration has been shown to be surprisingly effective in several pediatric brain tumors. This sensitivity to low-dose carboplatin is currently unexplainable by standard modeling (Mastangelo et al, 1995; Gaynon et al, 1990). Seven of 15 patients with recurrent PNET treated with weekly doses of carboplatin showed response to treatment (Allen et al, 1987). The majority of patients received 175 mg/m^2/week. Only low tissue levels of carboplatin are necessary to be radiosensitizing because the unbound drug has a half-life of 6 hours (Albers & Mason-Liddil, 1989). Therefore, the recent national cooperative group study chose to use 35 mg/m^2/day to establish sufficient radiosensitizing levels (Jakacki et al, 2006).

Daily administration of platinum during fractionated radiotherapy has shown positive results in solid tumors (Bartelink et al, 1986; Schaake-Konig et al, 1992; Jakacki et al, 2006). Concurrent chemotherapy and radiation with lower continuous dosing appears to have more effect on tumor cells than normal tissue with reduction of acute and late toxicities (Schaake-Konig et al, 1992; Steel, 1988; Jeremic et al, 1995; Jeremic et al, 1996). A trial of concurrent cisplatin and radiotherapy in patients with non-small cell lung cancer improved survival and local disease control compared to radiation alone (Schaake-Konig, 1992). Weekly cisplatin with radiation showed no significant difference. Esophagitis was not increased, but nausea and vomiting occurred in most patients. Head and neck cancer patients on a Phase I/II study of concurrent carboplatin and radiation had significantly improved survival rates than historical data with sequential chemoradiotherapy (Volling et al, 1992).

Glioblastoma multiforme patients were treated with Carboplatin (33mg/m^2) daily for five days during the first and fourth week of radiation therapy. Toxicity included Grade III and IV neutropenia in 25% of the patients and thrombocytopenia in 10% of patients. Neurotoxicity from radiation necrosis was not higher than in patients with radiation alone (Levin et al, 1995). Ausili-Cefari et al, gave

continuous infusion Carboplatin at a dose of 30 mg/m^2/day for either 14 or 21 days during radiation therapy to head and neck cancer patients. Only the patients who had carboplatin for 21 days had leukopenia and thrombocytopenia. There were no serious infections. Six of twelve patients developed mucositis, none requiring interruption of treatment (Ausili-Cefaro et al, 1995). A Phase I study of bi-weekly Carboplatin during radiation therapy for children with brain stem gliomas showed a mean tolerated dose of 280 mg/m^2/week for seven weeks (Allen et al, 1995).

Craniospinal irradiation has improved the survival rates for medulloblastoma, but it has also been implicated in poor quality of life related to impaired cognitive functioning that worsens over time (Packer, 1989). Radcliffe et al showed that whole-brain radiotherapy decreases IQ. Age is inversely correlated with loss of IQ. Children younger than 7 at diagnosis showed a significant loss of IQ points (Radcliffe et al, 1992).

Ribi, et al, (Ribi et al, 2005) followed 51 children who were consecutively diagnosed with medulloblastoma. Only two of the patients did not receive radiation because they were less than 3 years old. The other children received between 23.4-36.0 Gy craniospinal irradiation and with a boost of 48.0-55.0 Gy irradiation to the tumor bed. Significant deficits in neurocognitive functioning were seen in all of the patients. They had concurrent endocrine deficits (61%), neurological complications (72%), and significant school problems (72%)

Reduced dose craniospinal radiation has been shown to decrease the cognitive deficits. Mulhern et al demonstrated, in 22 children with medulloblastoma, that less severe neuropsychologic injury occurred when treated with only 23.4 Gy instead of 36 Gy craniospinal radiation. Once again, age was correlated with toxicity, with older children experiencing fewer cognitive deficits than younger children (Mulhern et al, 1998).

Goldwein, et al, treated 10 children diagnosed with medulloblastoma between 18 and 60 months of age with reduced craniospinal radiation . The patients received reduced dose craniospinal

radiation, a radiation boost to the tumor bed and standard maintenance chemotherapy. Survival at over 6 years was 70%, which is the accepted national survival rate for medulloblastoma with 36 Gy craniospinal radiation. The survivors had minimal neurocognitive damage, but did have decreased growth rates (Goldwein et al, 1996).

We therefore propose extending the benefits of reduced dose craniospinal radiation to metastatic medulloblastoma patients and high-risk, non-metastatic supratentorial PNET patients, and metastatic PNET patients by adding the concurrent carboplatin to the reduced dose radiation. Data regarding neuropsychologic outcome in children treated for non-metastatic medulloblastoma, with 36 Gy craniospinal radiation, and the same maintenance chemotherapy (Packer et al, 2006) is available, and will serve as a control group to assess the benefit of a reduced radiation dose.

4.0 METHODS

4.1 Eligibility Criteria

Inclusion Criteria

- Age greater than 3 years and less than 25 years.
- Patients with one of the following diagnoses by histological diagnoses and by head and spine MRI:
  - Classic histology metastatic medulloblastoma
  - Desmoplastic histology metastatic medulloblastoma
  - High-risk supratentorial, non-metastatic, PNET
  - Metastatic PNET
- Newly diagnosed patients who have not received prior therapy, with the exception of one short course of emergent chemotherapy in newly presenting patients with neurological compromise per provider decision
- Only patients who are expected to survive at least 6 weeks will be eligible for this study.

Exclusion Criteria

- Anaplastic histology will be excluded
- Patients who are pregnant may not be treated on this study

4.2 Subject Enrollment

Approximately 10 subjects will be enrolled locally at Children's Hospital Colorado. Eligible subjects will be offered participation in the study by their primary physician through the Neuro-Oncology Program at Children's Hospital Colorado. The subjects may be inpatients or outpatients.

4.3 Informed Consent Procedure

The investigator (or designee) will obtain written informed consent/assent from each subject or their authorized representative who participates in the study, before the initiation of any study procedures. All physicians, nurses, and study coordinators who are involved with the study and may perform any or all parts of the consent process have been educated in research principles and certified by taking the applicable COMIRB education course(s). The consent/assent will be explained in an environment that is private, quiet, and conducive to effective communication. Explanation will be given at the level of comprehension of the consentee. A dialogue between the subject and/or parent and the investigator will confirm the understanding and agreement to participate.

Non-English Speaking Subjects

This study will follow the COMIRB guidelines regarding Non-English speaking subjects, per the following from the COMIRB Instructions for Clinical Investigators:

45 CFR 46.117 (b)(2) permits oral presentation of informed consent in conjunction with a short form stating that the elements of informed consent have been presented orally, for studies that will include non-English speaking subjects but not purposely recruit them. A study is permitted to utilize the short

form up to three times in the same language. If a 4th subject is to be enrolled then a translation of the entire consent form should be provided.

After the English version is approved, a translated consent form should be obtained by the investigator and submitted to COMIRB. The credentials of the translator must be provided to COMIRB. The translator must have expertise (native language or evidence of fluency) in the language including medical and legal terminology, in order to translate consent forms. When the translated consent form is used with a subject, the person obtaining consent and the subject or their representative will sign the non-English consent form.

A translator fluent in the subject's language and English must read the consent summary to the subject or their representative. A written summary of what is presented orally is also required. A witness to the oral presentation is required, and the translator can also serve in this role. The subject or their representative and the witness (translator) must sign the Short Form. The person obtaining consent as authorized under the protocol and the witness (translator) must sign the Consent Summary. The subject must be given copies of the Short Form document and the Consent Summary. The investigator must have a plan for how to answer the subject's questions and assess comprehension in the subjects' native language. The subject or his/her representative walks away with: (1) the short form written consent in the subject's language; (2) the long standard consent in English; (3) a copy of the summary of the oral presentation.

Forms required for oral presentation of consent:

- Short Form. This must state that the **elements** of consent have been presented orally to the subject and it must be in the language the subject is fluent in. A template of the Short Form is available in a variety of languages on the COMIRB web site under Forms. The subject or their representative and the witness, who in most cases is the translator, must sign this form.

  Consent Summary. The COMIRB approved English language consent form can serve as

the consent summary. The person obtaining consent and the witness (translator) should sign this.

Health outcomes on all subjects will be studied, but only an English-speaking subset will be measured for neuropsychologic outcomes due to the limitations of the testing measures used in this study in order to compare to the control group.

4.4 Confidentiality

The clinical and laboratory data for each patient are part of their medical records at Children's Hospital Colorado. Laboratory data are computerized at CHCO and accessible to authorized staff that have a laboratory password. Patient data will also be entered into Children's Hospital Colorado Neuro-Oncology Program database. This information will be used by the principal investigator for data collection and analysis and will only be accessible to qualified staff working on this research project. The database is a secure, password-protected database. Completed data forms for each patient on study at Children's Hospital Colorado will be kept in locked cabinets, accessible only to study team members. The clinical research associates will monitor the level of authorization/consent signed by the patient to assure that authorization has been obtained for release of all data that are released.

4.5 HIPAA Authorization Procedure

Written authorization will be obtained at the time the consent is obtained, as this study will collect protected health information from the subjects. The principal investigator(s) or qualified designee will explain the HIPAA regulations in the combined consent/HIPAA authorization form. The clinical research associates will assure that the consent/HIPAA authorization form has been properly signed and dated prior to study entry, and that the subject/parent receives a copy of the signed and dated form. The program database will contain the date the consent/HIPAA authorization form was signed. Information will be released only to those specified in the consent/HIPAA authorization form.

5.0 TREATMENT PROGRAM

5.1 Chemoradiotherapy

Within 28 days of diagnosis, patients will start radiation therapy, at a dose of 24 Gy. The craniospinal axis will be treated first. Daily carboplatin will be given at 35 mg/m^2 IV over 15-20 minutes Monday through Friday, approximately 1-4 hours prior to radiation for 6 weeks (total of 30 doses). Weekly Vincristine will be given at 1.5 mg/m^2 (standard therapy) for 6 weeks.

Following radiation, patients will receive the current national standard of maintenance chemotherapy with a cisplatin backbone. Maintenance chemotherapy will always reflect the national cooperative group's evidence-based standard of care. Subjects will be followed during maintenance, but no research testing will be conducted during this standard of care chemotherapy. The first dose of carboplatin should be administered on the first day of radiation therapy, unless the patient needs emergent treatment, in which case carboplatin may be administered prior to the first day of radiation therapy. Carboplatin will be administered in 25 ml NS IV over 15 minutes approximately 1-4 hours prior to radiation therapy. This should be sufficient time for patients who may require sedation or who travel to another facility.

If a radiation treatment is not given, carboplatin should be held as well. If a dose of carboplatin is given and radiation therapy is NOT administered due to sedation or technical issues, the carboplatin dose should not be made up at the end of radiation (i.e. no more than 30 doses of carboplatin should be given). Since there are 31 fractions of radiation, the last radiation treatment will not be preceded by a dose of carboplatin.

Pregnancy tests will be done per standard of care protocol at screening and prior to any treatments. Subjects should not be pregnant prior to starting the study, or become pregnant, nurse a child, or father a baby while on this study because the study treatment may harm an unborn baby, nursing child, or pregnant female. Subjects must use effective birth control while on this study.

Subjects will be counseled by the medical staff regarding this issue as necessary. Any pregnancy that inadvertently occurs in a study subject or a partner of a subject must be reported to COMIRB as an unanticipated problem with the required documents and the study will be re-reviewed at that time.

5.2 Supportive Care During Chemoradiotherapy

5.21 G-CSF During Radiotherapy

CBCs will be obtained weekly. If ANC is less than or equal to 500/microliter, G-CSF will be administered 5 mcg/kg/day subcutaneously or IV until ANC is greater than 500. In the event of potentially life-threatening infection with neutropenia, G-CSF may be increased to 5 mcg/kg/dose twice daily.

Significant myelosuppression may occur, particularly during the last two-three weeks of radiation, although this has been relatively infrequent. However, radiation should not be withheld for myelosuppression alone. Radiation should be continued even if the patient is hospitalized with fever and neutropenia as long as the patient is clinically stable. Administration of the boost should not be substituted for craniospinal radiation in the face of low counts.

5.22 Platelets

Platelets should be transfused as clinically indicated, and in all patients with counts <10,000/microliter.

5.23 Red Blood Cells

Patients should be transfused as necessary to maintain a hemoglobin greater than or equal to 8.

5.24 Pneumocystis Prophylaxis

Pneumocystis prophylaxis with trimethoprim/sulfamethoxazole (5 mg/kg/day of trimethoprim in two divided doses given 2 consecutive days per week) is recommended for all patients during chemoradiotherapy, and should be continued during the maintenance chemotherapy. Pentamidine (4 mg/kg every 3 weeks) is recommended for patients who are allergic to trimethoprim/sulfamethoxazole.

5.25 Nutrition

Patients are to be weighed weekly. If there is greater than 10% weight loss, megestrol (megace) at 10 mg/kg in two divided doses or nutritional support, either enterally or parenterally, should be considered.

5.26 Fungal Prophylaxis

Patients on this protocol are likely to develop mucositis and esophagitis and will be more susceptible to oral and esophageal candidiasis. In the event of candidiasis, Fluconazole (3 mg/kg/day) is recommended.

5.27 Emesis

Although carboplatin at these doses is unlikely to cause nausea and/or vomiting, patients may experience nausea and/or vomiting during the first few craniospinal radiation treatments. Prophylactic anti-emetic therapy with either Ondansetron or Granisetron should be used, at least during the first week.

5.28 Maintenance chemotherapy

Maintenance chemotherapy will commence six weeks after radiation has been completed, or when ANC > 1000/μL and platelets >100,000/μL, whichever occurs last.

5.3 Dose Modification

5.31 Hematologic Toxicity

Patients may develop myelosuppression, especially during the last 2-3 weeks of radiation therapy. See sections 5.21-5.23. No dose modifications of Carboplatin or radiation therapy will be made.

6.0 REQUIRED OBSERVATIONS

6.1 Pre-Treatment and During Chemoradiotherapy

Evaluation	Pre-Study	Weeks 1-3	Weeks 4-6	Weeks 7-9 (After start of XRT)	Weeks 10-12 (After start of XRT)
CBC with diff, platelets	X	weekly	weekly	if clinically indicated%	if clinically indicated
Physical exam neuro exam*, height, weight, Lansky/Karnofsky performance status*	X	weekly	weekly		
Electrolytes, Ca, Creatinine, BUN, SGOT, bilirubin	X	q o week	q o week	if clinically indicated	
MRI of the head (T2-weighted imaging and T1-weighted imaging pre- and post-contrast) and spine with contrast	X#				X+ (week 10)
Lumbar CSF cytology@	X				X+
Audiogram	X				X
Neuropsychologic Testing				X!	

\+ Spine MRI and cytology to be done only if initially positive

\# Post-op MRI should be done within 72 hours of surgery. For patients who undergo stereotactic biopsy only, post-op MRI is not required. Spinal MRI is required within 28 days of surgery if done post-operatively and within 7 days of surgery if done pre-op. (If MRI scan is performed within 7 days prior to surgery, then only a post-contrast examination is required). A pre-operative spinal MRI scan is preferable for patients with posterior fossa tumors because surgically-induced inflammation/blood can be difficult to distinguish from tumor.

% If counts are low, CBC should be performed twice weekly.

@ Ventricular CSF (either pre-or post-op) may be used only if a post-operative spinal tap is contraindicated. If a spinal tap is contraindicated and there is no ventricular CSF available, then CSF cytology can be waived for patients with supratentorial tumors or if there is documentation of spinal subarachnoid metastases (M3).

*See Appendix 1 for neurological exam guidelines and Appendix 2 for Karnofsky/Lansky performance scales.

! Baseline neuropsychologic testing will be done between 3 – 6 months post-radiation, as was done on the 9961 protocol . An abbreviated battery will be utilized. See Appendix 3 for testing protocols.

6.2 Pre-Study Examination:

- A full clinical examination with particular detail to neurological deficits must be carried out at diagnosis. A formal neurological examination should be performed on entrance to study. It is imperative that neurological deterioration on therapy be adequately documented.

- Imaging: An MRI 3-dimensional assessment of head (with and without contrast) and spine (with contrast) at diagnosis.
- CSF involvement is defined as presence of tumor cells in the lumbar CSF. Lumbar puncture will be obtained > 7 days after surgery at diagnosis. CSF should be obtained > 7 days post-operatively for posterior fossa tumors to minimize the risk of false positive results that do not represent true, viable metastases. Tumor cells in the cisternal CSF are not considered prognostic and may not be considered in the definition of CSF involvement.
- Hematology/biochemistry (CBC with differential and platelet count; Chemistry panel - Electrolytes, calcium, creatinine, BUN, SGOT, bilirubin,).
- A baseline audiogram will be obtained.

6.3 Evaluation During Treatment

- A physical exam, including a formal neurological exam (see Appendix 1) and height, weight, and performance status (see Appendix 2) will be performed weekly during chemoradiotherapy.
  Hematology: Regular CBCs with differential and platelet count will be performed weekly during chemoradiotherapy. If the ANC falls below 1000, CBC should be checked every 3-5 days. In the event of potentially life-threatening infection with neutropenia, G-CSF may be increased to 5 mcg/kg/dose twice daily.
- Audiogram: Will be repeated 4-6 weeks after the completion of chemoradiotherapy.
- Chemistry (Electrolytes, calcium, creatinine, BUN, SGOT, and bilirubin) will be performed every other week during weeks 1-9.
- Imaging: A MRI scan of the head (with and without contrast) and spine (with contrast) should be performed at 4-6 weeks after the completion of chemoradiotherapy.
- CSF involvement at diagnosis: A lumbar puncture will be repeated 4-6 weeks after the completion of chemoradiotherapy.

- Neuropsychologic testing will be performed 3-6 months after radiation is completed (see Appendix 3).

6.4 Evaluation Following Protocol Therapy

Starting from the end of radiation therapy until 5 years after the end of radiation therapy, physical exam (as described above), CBCs and blood chemistry (if clinically indicated), MRIs of the head and spine, lumbar punctures, audiograms, neuropsychologic testing and thyroid function tests will be performed according to the intervals in the table in section 6.5.

6.5 Required Observations Following Protocol Therapy

Evaluation (Dated from the End of RT)	**4 mos**	**6 mos**	**8 mos**	**12 mos**	**15 mos**	**18 mos**	**21 mos**	**24 mos**	**30 mos**	**36 mos**	**42 mos**	**48 mos**	**60 mos**	**At Relapse/ Disease Progression**
Physical exam, neuro exam*, height, weight, Lansky/Karnofsky performance status*	X	X	X	X	X	X	X	X	X	X	X	X	X	
CBC with diff, platelets	X	X	X	X									X	
MRI of the head (pre- and post-contrast)	X		X	X	X	X	X	X	X	X	X	X	X	X
MRI of the spine with contrast+	X		X	X	X	X	X	X	X	X	X	X	X	X
Lumbar CSF cytology+	X			X				X		X				X
Audiogram		X		X				X		X		X	X	
Thyroid Function Evaluation (Free T_4 and TSH)		X		X				X		X		X	X	
Neuropsychologic Testing								X!					X!	

!Neuropsychologic testing: See testing requirements in Appendix 3

+ Spine MRI and cytology to be done only if initially positive

*See Appendix 1 for neurological exam guidelines and Appendix 2 for Karnofsky/Lansky performance scales.

7.0 DRUG INFORMATION

7.1 Vincristine (Oncovin)

NSC-67574. Commercially available.

7.12 Formulation

Clear liquid, 1 mg, 2 mg, and 5 mg vials.

7.13 Storage

Refrigerate. Protect from light.

7.14 Stability

Multiple-dose containers with preservatives are stable 30 days after opening if refrigerated.

7.15 Toxicities

Neuromuscular effects, peripheral neuropathy, jaw pain, abdominal pain, mucositis, nausea and vomiting, hypersensitivity, urinary retention, optic atrophy (rare), blindness (rare), constipation, loss of deep tendon reflexes, foot and wrist drop, paresthesia, alopecia, convulsion (rare), hyponatremia (SIADH), severe soft tissue damage if extravasated. Vincristine is very irritating and must not be given IM, subcutaneously or intrathecally. Intrathecal administration of vincristine almost always has resulted in death.

7.2 Carboplatin (Paraplatin)

NSC-241240. Commercially available.

7.21 Formulation

Lyophilized powder, 50 mg, 150 mg, and 450 mg of Carboplatin per vial. Each vial contains equal parts by weight of carboplatin and mannitol.

7.22 Storage

Room temperature. Protect from light.

7.23 Reconstitution

Reconstitute each vial with NS, sterile water, or D5W to achieve a final concentration of 10 mg/ml. Further dilution to concentrations as low as 0.5 mg/ml with NS or D5W is acceptable.

7.24 Stability

Discard infusion solution 8 hours after preparation, since it contains no antibacterial preservative.

7.25 Toxicities

Myelosuppression, nausea and vomiting, transient liver function abnormalities, paresthesia and high frequency hearing loss, abnormalities in serum creatinine and creatinine clearance, proteinuria, hypocalcemia, and hypomagnesemia.

8.0 RESPONSE CRITERIA

The same method used to quantitate tumor status prior to starting this study must be used to measure tumor status after treatment. Therefore, only MRI scans will be used to determine response or progression of disease.

- Complete Response (CR): Complete resolution of tumor on MRI scan
- Partial Response (PR): A reduction of at least 50% in tumor area of bidimensional measurable lesions. In addition, there can be no appearance of new lesions or progression of any lesion.
- Stable Disease (SD): A decrease of less than 50% or an increase of less than 25% in the tumor area of bidimensional measurable lesions .
- Progressive Disease: Greater than a 25% increase in the bidimensional tumor area compared to the immediate pre-study area or compared to area of best prior response at that site, or the reappearance of tumor in sites of involvement which had responded completely to therapy (including surgery), or appearance of tumor in a previously uninvolved area.

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY, FOLLOW-UP, AND OFF STUDY CRITERIA

9.1 Criteria for Removal from Protocol Therapy

Patients may be removed from protocol therapy prior to completion under the following circumstances:

a) Disease relapse/progression (see Section 8.0)

b) Parent/patient request

c) Death

d) Physician or investigator's discretion

Discontinuation for other reasons will be considered protocol deviations.

9.2 Removal from Protocol Follow-up

Patients may be removed from protocol specified follow-up under the following circumstances:

a) Death

b) Parent/patient request

c) Entry onto a sanctioned second line therapeutic study or follow-up study.

10.0 NEURORADIOLOGY GUIDELINES

10.1 Whole Brain MRI With and Without Contrast

To document the degree of residual tumor, postoperative MRI scan, with and without contrast, must be done prior to beginning therapy. For patients who undergo stereotactic biopsy only, a post-operative MRI is not required. For patients with M2 and M3 disease, a post-op MRI is strongly encouraged, but not mandatory.

Postoperative MRI should be done within 72 hours of surgery, when there is less edema or postoperative enhancement, which can make measurements of residual tumor difficult. An MRI with

and without contrast should be done 4 weeks after the completion of radiotherapy, prior to cycle 4 and one month after cycle 6 of maintenance chemotherapy, during follow-up, and at relapse .

10.2 Pre- or Post-operative Spinal Axis Imaging

An MRI with and without gadolinium of the entire spine (through the inferior extent of the thecal sac) is required either 7 days prior to or within 28 days after surgery and at relapse. If an MRI scan is performed within 7 days prior to surgery, then only a post-contrast examination is necessary. **Note: a pre-operative MRI scan of the spine is preferable for patients with posterior fossa tumors because surgically-induced inflammation/blood can be difficult to distinguish from tumor.**

11.0 NEUROSURGICAL GUIDELINES

11.1 Types of Surgery

A craniotomy or craniectomy is necessary to remove the bulk of the tumor, to reestablish CSF circulation, and to provide tissue for diagnosis. The goal of the operation should be a gross total resection unless involvement of vital structures or widely disseminated disease makes this impractical. In the posterior fossa, a gross total resection should be accomplished unless there is invasion of the floor of the fourth ventricle, middle cerebellar peduncle, cerebellar pontine angle, or other brain stem structures. In the supratentorial space, a gross total resection should be accomplished unless the tumor invades deep structures, such as the hypothalamus, or functionally important cortex, such as the motor or speech cortex. If the tumor appears near functionally important cortex on the pre-operative scan, consideration should be given to intraoperative cortical mapping with the aim of sparing functional cortex while achieving the greatest tumor resection possible.

If the post-operative MRI scan (obtained within 72 hours of the operation) reveals residual resectable tumor, a second operation should be considered to remove the remaining tumor. Few, if any, patients should be entered into this study with biopsy only or partial resections.

Biopsy alone, with no attempt at resection, may be associated with a statistically worse survival and should not be done except in the setting of widely metastatic disease and a small primary tumor. No patient will be entered without a diagnosis established by microscopic examination of tumor tissue.

11.2 Staging Criteria

11.21 Extent of Resection/Surgical Confirmation

a) Biopsy Only: If tumor removal is less than 10% of the total tumor mass, this will be considered a biopsy only.

b) Partial Resection: The surgical removal of greater than 10%, but less than 50%, of the tumor mass.

c) Sub-total Resection: The surgical removal of greater than 50%, but less than 95%, of the tumor mass.

d) Radical Subtotal Resection (Near Total): The surgical removal of greater than 95%, but less than 100% of the tumor mass.

e) "Gross Total" Resection: No visible tumor is left at the time of surgery and is confirmed by postoperative CT or MRI.

11.22 Metastasis Stage (M0-M4)

The surgeon should inspect the regional leptomeninges and a decision should be made as to whether metastatic nodules are present in the arachnoid or whether the entire leptomeningeal surface is infiltrated with tumor. If there is any question, a small segment of arachnoid should be excised and sent as a separate specimen.

11.23 MRI Confirmation

All patients will have confirmation of the neurosurgical assessment of the extent of resection with a postoperative MRI scan, without and with contrast. This scan should be carried out within 72 hours postoperatively. Bidimensional measurements of residual tumor volume should be obtained. For

patients who undergo stereotactic biopsy only, a post-operative MRI is not required. For patients with M2 and M3 disease, a post-op MRI is strongly encouraged, but not mandatory.

11.3 Peri-operative Corticosteroids

Some patients with large tumors may require corticosteroid therapy preoperatively to reduce associated cerebral edema.

a) Usual corticosteroid dosage is 0.25 to 1 mg/kg/day of dexamethasone, in divided doses, every 4-6 hours.

b) Corticosteroids may be continued during the peri-operative period, but the dosage, dose interval and duration of steroid therapy must be noted, and every attempt made to taper and discontinue corticosteroid therapy as soon as clinically feasible.

11.4 Pathology Studies

As much tumor as possible should be sent for pathology and biologic studies. Tissue should go directly to the institutional pathologist in saline (wrapped towel) prior to fixation in formalin for histologic diagnosis.

11.5 Shunts

a) Children may need preoperative external ventricular drains, if they are symptomatic because of tumor-induced hydrocephalus.

b) After removal of the tumor and the external drains, approximately 30% of patients with medulloblastoma/PNET will require a CSF shunt because of permanent hydrocephalus.

c) The routine use of pre-operative shunts or shunt filters is not encouraged.

12.0 RADIATION THERAPY GUIDELINES

The craniospinal and boost radiation techniques outlined below are standard for this tumor.

ATTENTION: The radiotherapy guidelines for this protocol do not allow for treatment breaks except in the setting of clinical instability.

12.1 Timing of Radiation Therapy

All patients shall receive irradiation to the cranio-spinal axis (CSA) followed by a boost to the primary tumor site (posterior fossa or supratentorial) as well as to CNS metastatic sites. All patients shall begin radiation treatments after registration on study and within 35 days of definitive surgery.

12.2 Equipment

12.21 Modality

Photon irradiation shall be used.

12.22 Energy

The cranial field should be treated with megavoltage photons with energies in the range of 4 – 6 MV. The primary site boost will usually be given with similar energy, but for centrally located primary tumors, the boost may be given with a photon beam of higher energy. In such cases, an isodose plan should be submitted with the quality assurance material. Photon of energy 4 to 6 MV will generally be used for spinal irradiation but electrons of suitable energy may be used.

12.23 Geometry

All patients must be treated on isocentric machines. All machines must have a minimum source- to-axis distance (SAD) of 80 cm. Treatments may be given with fixed SSD techniques.

12.24 Simulator

All patients must be simulated on a dedicated radiation therapy simulator.

12.25 Immobilization Devices

For craniospinal irradiation, immobilization devices such as head holders or custom mold are required. Head immobilization with a thermoplastic mask or head frame is required when 3D treatment planning is used. The immobilization device should limit daily motion to a maximum of ± 3– 5mm.

12.3 Treatment Volume Anatomical Description

12.31 Treatment Volumes

Definitions:

• Gross Target Volumes (GTV): The Gross Target Volume (GTV) is based upon the T1 weighted MRI with and without Gadolinium contrast. Identification of the GTV shall be based upon pre-operative extent and anatomic shifts or changes after surgery. The GTV should include any residual enhancing tumor mass and the wall of the resection cavity.

• Clinical Target Volume (CTV): The Clinical Target Volume (CTV) is defined as the GTV plus a 1.5-cm margin

• Planning Target Volumes (PTV): The Planning Target Volume (PTV) margin should be an additional 0.3 to 0.5 cm around the CTV, depending on the setup error of the treatment modality used. In treatment planning, shielding of critical structures should be attempted. At least 95% of the prescribed study dose (55.8 Gy) must encompass at least 95% of the PTV as shown by DVH. No part of the PTV should receive less than 50 Gy.

• Treated Volume (TV): The volume enclosed by an isodose surface that is selected and specified by the radiation oncologist to which the prescribed dose is delivered.

12.32 Treatment Volume

The target volume for the initial portion of the treatment is the entire cranio-spinal axis (the entire subarachnoid space). The target volume for the boost is the tumor bed and the residual tumor if the primary site is in the infratentorial region of the brain. The target volume for the boost for supratentorial tumors is 1 cm around the tumor as seen on the pre-surgical MRI scan. Metastatic tumors will receive boost irradiation with a 1 cm margin around the tumor as seen on a pretreatment MRI scan. 3D treatment planning may be used to plan the boost portion of the treatment.

12.33 Cranio-Spinal Axis

The cranio-spinal axis comprises the whole brain as well as the spinal cord and thecal sac. The whole brain treatment volume should extend anteriorly to include the entire frontal lobe and cribriform plate region. The superior orbital tissue (but not the posterior globe) should be included in the volume. The treatment volume should extend at least 0.5 cm inferiorly below the base of the skull. The volume should extend inferiorly to the superior border of the spinal field. The spinal treatment volume should extend laterally to cover the recesses of the entire vertebral bodies, with at least a 1.0 cm margin on either side. It should extend superiorly to the border with the cranial field and inferiorly 1-2 cm below the termination of the thecal sac. This position should be determined from a sagittal MRI and will always be at least as low as the inferior border of the S2 and may extend to S4. A "spade" field may be required to obtain a 1.0 cm margin around the subarachnoid space at the level of the sacrum. The objective is to include the nerve roots as they exit the neural foramina.

12.34 Posterior Fossa Boost

The posterior fossa boost will be a conformal limited target volume boost. 3D-based treatment planning is mandatory for these volumes. The Gross Target Volume (GTV) is based upon the T1 weighted MRI with and without Gadolinium contrast. Identification of the GTV shall be based upon pre-operative extent and anatomic shifts or changes after surgery. The GTV should include any residual enhancing tumor mass and the wall of the resection cavity. The Clinical Target Volume (CTV) is defined as the GTV plus a 1.5-cm margin except at bone or tentorial interface (where it remains within the confines of the posterior fossa). The Planning Target Volume (PTV) margin should be an additional 0.3 to 0.5 cm around the CTV, depending on the setup error of the treatment modality used. In treatment planning, shielding of critical structures should be attempted. At least 95% of the prescribed study dose (55.8 Gy) must encompass at least 95% of the PTV as shown by DVH. No part of the PTV should receive less than 50 Gy.

12.35 Supratentorial Boost

The treatment volume for a supratentorial boost will be defined using a 1 cm margin around the presurgical MRI defined tumor volume. In the event of proximity to normal tissue structures, this margin may be reduced to 0.5 cm to allow for shielding of critical structures. If the margins are reduced to 0.5 cm, this should be clearly stated and justified in the submitted QA documentation. As the total dose to the optic chiasm and both optic nerves should not exceed 50.4 Gy, these structures should be blocked accordingly. A supratentorial boost set up to treat metastatic disease (M2) should meet the same guidelines as that for a boost for a primary supratentorial tumor.

12.36 Spinal Boost(s)

For patients with spinal deposits of disease, focal boosts to the pre-chemotherapy volume with 1cm margin (target volume) will be employed.

12.4 Three Dimensional Treatment Planning

Three dimensional (3D) treatment planning will be used for the whole brain and spinal axis treatments as well as any boosts.

12.41 Planning System Requirements

Any volume based treatment system e.g., conformal radiation treatments (co-planar or non-coplanar), stereotactic radiotherapy, intensity modulated radiotherapy, and proton therapy, is allowable if it satisfies the following criteria. Brachytherapy and stereotactic radiosurgery are not allowable.

12.42 Treatment Planning

Radiotherapy treatment planning will be based upon contrast-enhanced CT or MRI scan. This scan should be performed in the axial plane at a spacing of no more than 3mm. The scan should encompass the entire cranium and the cervical spine down to the level of at least C3.

12.43 Normal Tissue Volumes

The following normal tissue will be defined on the treatment planning scan, and dose-volume histogram data will be reviewed for these structures:

1) L, R Cochlear and vestibular apparatus bilaterally

2) Supratentorial brain

3) Pituitary gland

4) L, R Optic nerves and chiasm

12.44 Dose Prescription

The radiation dose will be calculated and normalized to the isocenter of the beams used for treatment. The 95% isodose surface will be required to completely encompass the PTV.

12.5 Treatment Dose

12.51 Dose Definition

12.511 Absorbed Dose Specification

All doses shall be specified as cGy to water.

12.512 Tissue Inhomogeneity Consideration

Inhomogeneity correction should be made for bone and lung transmission.

12.52 Prescription Point

12.521 Brain

If the brain is treated by parallel-opposed fields, the dose should be defined at a point along the central axis midway between the lateral entrance points (midplane). If an independent jaw or half-beam block technique is used, the dose should be specified at an off-axis point that corresponds to the midplane point used for a conventional "opposed lateral" treatment set-up.

12.522 Spine

The dose to the spine should be prescribed along the central axis at a depth representing the posterior margin of the vertebral bodies as determined by cross-table lateral x-rays, MRI or CT scans.

12.523 Primary Site Boost

For 2D treatment plans the prescription point should be in the center of the target volume, i.e. along the central axis of the opposed beams, midway between the two entrance points. Note that the dose contribution to the posterior fossa dose from the whole brain fields should be considered equal to the dose prescribed to the whole brain. Correction for decreased separation should not be made. For 3D treatment plans, the prescription point should be as defined in Section 12.45.

12.524 Other Boost Sites

The dose to other boost sites will be calculated at the mid-tumor point calculated on the central axis of the boost fields.

12.53 Total Treatment Dose

12.531 Craniospinal Axis

All patients will receive 23.4 Gy to the craniospinal axis.

12.532 Primary Site Boost

All patients with primary tumor in the posterior fossa will receive a boost of 32.4 Gy to the posterior fossa. All patients with a supratentorial primary tumor will receive a boost 32.4 Gy to the volume described in section 12.3. As noted there, the total dose to the optic chiasm and both optic nerves should be limited to 50.4 Gy. In addition, if the boost volume occupies more than 2/3 of the supratentorial compartment, the boost dose should be limited to 27 Gy.

12.533 Metastatic Site Boost

Patients with M1 disease will receive no additional boost. Patients with M2 disease (intracranial subarachnoid disease) will receive boosts of 32.4 Gy to focal areas of supratentorial or posterior fossa metastatic disease. If the volume of a boost to the supratentorial compartment exceeds 2/3 of the

supratentorial compartment volume, the boost will be limited to 27 Gy. The boost dose to the optic chiasm and both optic nerves must be limited to 27 Gy. 3D treatment planning may be used for boosting M2 disease. If 3D planning is used, definitions boost volumes for M2 disease will be the same as specified for boosts to the primary tumor. Patients with M3 disease (spinal deposits of disease) are subdivided into those with diffuse disease and those with focal disease. Diffuse spinal disease is defined as radiographically visible multiple sites of disease in each of at least 3 out of 4 spinal regions (i.e., cervical, thoracic, lumbar or sacral).

If there is diffuse involvement of the spine, the entire spine will be treated to 23.4 Gy. An MRI scan of the spine should be performed when the spine has received 23.4 Gy, and areas of visible disease remaining at that point should be boosted to 45 Gy when above the termination of the spinal cord and 50.4 Gy when below the termination of the cord. If there are focal areas of spinal deposits which do not meet the definition of diffuse involvement defined above, the entire spine will be treated to 23.4 Gy. The focal areas of tumor seen on the initial spinal MRI will be boosted to 45 Gy. Focal deposits below the termination of the cord as defined by the initial MRI will be boosted to 50.4 Gy. The margin for boosting metastatic deposits will be at least 7 mm, and preferably 10 mm.

12.54 Time Dose Consideration

12.541 Daily Dose

The daily dose to the prescription points should be 180 cGy. Corrections for a higher contribution of dose to the PF or upper cervical spinal cord from whole brain treatment should not be made.

12.542 Fractionation

All radiation fields should be treated once each day and treatments should be given 5 days per week.

12.543 Unplanned Treatment Breaks

Interruption or discontinuation of radiation will be permitted ONLY for:

1) Severe medical conditions precluding delivery of radiation. This does not include straightforward fever and neutropenia admissions (i.e. radiation therapy and carboplatin should continue to be administered without interruption). If radiation cannot be resumed within two weeks of discontinuation, the study chair should be informed and the patient will be off study.

2) Hematologic toxicity alone should NOT result in unplanned treatment breaks.

Only when the patient is clinically unstable, should radiation therapy be held.

ONCE CRANIOSPINAL RADIATION THERAPY IS STARTED, IT IS TO BE COMPLETED WITHOUT INTERRUPTION (I.E. BOOST RADIATION SHOULD NOT BE ADMINISTERED INSTEAD OF CRANIOSPINAL RADIATION UNTIL COUNTS RECOVER).

12.55 Dose Homogeneity and Reference Points

12.551 Brain, Posterior Fossa and Supratentorial Boost

Throughout the central plane, a dose homogeneity of +5% relative to the prescription point is required. A correction for the higher contribution of dose to the PF and upper cervical spinal cord from whole brain treatment is not required. In no instance will homogeneity exceeding 10% in the central plane be acceptable.

12.552 Spine

The maximum dose variation along the longitudinal axis of the spinal cord should be +5%. Tissue compensations may be required to achieve this degree of dose uniformity. The dose to the spinal cord at the level of T2 and L3 should be recorded as off-axis points.

12.553 Uniformity Reference Points:

The reference point for the posterior fossa due to the whole brain radiation will be the midplane of the skull at a point that will be along the central axis of the lateral posterior fossa boost points. The posterior margin of the vertebral body representing the anterior margin of the spinal canal will

represent the spinal cord uniformity reference point. The off-axis reference dose will be calculated at the anterior margin of the spinal canal at T2 and L3. The midplane of the cranium will be used as the uniformity reference point for the cranium.

12.554 Allowed Methods of Dose Compensation

To remain within the acceptable range of uniformity, the areas receiving higher dose may be blocked for the last few fractions of treatment. Wedges or tissue compensators may be used at the discretion of the individual radiation oncologist.

12.6 Treatment Technique

12.61 Patient Position

For cranio-spinal irradiation the patient should be treated prone. The neck should be extended sufficiently to keep the mandible out of the exit beam of the spinal field but not so much as to exceed the dose uniformity specifications of the spinal field. Immobilization devices such as head holders or custom molds are required for 3D treatment plans. For boosting the posterior fossa or supratentorial sites, the patient may be in either the prone or supine position.

12.62 Whole Brain Irradiation

Parallel-opposed fields may be used. Alternatively, the field center can be placed near the match line with the spinal field and an independent jaw or half-beam block technique utilized. This method decreases overlap at the match line. The collimation of the brain field should be rotated to match the divergence of the spinal field according to the equation:

$$\text{Collimator angle} = \tan^{-1} \frac{\text{spine length}/2}{\text{Source-to-axis distance}}$$

The lateral fields may be angled posteriorly to spare the collateral lens, but, if this is done, great care must be taken to assure adequate coverage of the cribriform plate. Custom divergent blocking of at

least 5 HVL should be used to shape the brain field at the base of the skull and around the eyes. The brain field should extend to at least 1 cm beyond the periphery of the scalp.

12.63 Spinal Cord

Preferably, the spinal volume should be treated with a single posterior field. An extended SSD is preferable to the use of adjacent ports. If adjacent ports are necessary, the 50% decrement should cross at the posterior margins of the vertebral body. It is preferable that the match line be placed inferior to the spinal cord (below L2) and should be moved every 900 cGy. Custom blocking may be required at the inferior border of the spine. An attempt should be made to avoid exit through the jaw and mouth from the spinal field by hyperextending the neck, if the curvature does not compromise dose homogeneity.

12.64 Abutting Fields

With the use of collimator rotation and an independent jaw technique, the cranial and spinal fields may be directly abutted (light fields). Many radiation oncologists, though, are more comfortable with a gap between the cranial and spinal light fields. A gap of 0.5 cm is allowed on this protocol. The match line should be moved three times during treatment of the cranio-spinal axis. Also, a penumbra broadening "match line wedge" or a dynamic wedge may be used. The match line should never overlap the posterior fossa boost. Therefore, it is recommended that the first match line lie just above the shoulder, and the last 3-cm higher. Alternatively, the first match point could begin at the superior point and end at the inferior point.

12.65 Primary Site Boost

For patients treated with posterior fossa primary sites, the primary site boost should be treated by a pair of opposed lateral fields. For patients with supratentorial primary sites, or patients planned with 3D techniques, any appropriate configuration of fields is allowable.

12.66 Boosts to Metastatic Sites

Intracranial metastases can be boosted by any appropriate technique. Spinal metastases should be treated with a posterior field.

12.67 Field Shaping

Individually cut blocks to shape the skull field at the base of the skull and eye are strongly recommended. Similarly, field shaping may be required at the inferior border of the spinal field.

12.7 Quality Review

A retrospective quality review of radiotherapy planning and treatment will be performed by an independent radiologist.

13.0 STATISTICAL CONSIDERATIONS

This is a pilot study of concurrent carboplatin (CARBO), vincristine (VCR), and radiation therapy (XRT) followed by standard of care maintenance VCR and cyclophosphamide (CPM) ± cisplatin (CDDP) in children aged 3 to 25 years with metastatic medulloblastoma, high risk PNET and metastatic PNET. Eligible patients comprise those with supratentorial PNET and infratentorial PNET/MB with initial stage M1-M4 or >1.5cc residual tumor remaining after surgery and classical histology.

The primary objective of the protocol and the statistical analysis is to obtain preliminary estimates of event free survival (EFS) and to demonstrate less decrement in intellectual function in preparation for a future Phase III randomized trial including these treatments.

Statistical considerations for the primary objective are addressed below.

13.1 Patient Accrual

The Neuro-Oncology Program at Children's Hospital Colorado has seen an average of 5 patients per year with metastatic medulloblastoma, high risk PNET and metastatic PNET. We expect to enroll 10

patients. The current standard of care CCG 9961 was based on a pilot study of 10 patients (Goldwein et al, 1996).

13.2 Study Duration

We originally anticipated that it would require approximately 24 months to complete accrual to this study. However, at this time we are more accurately anticipating to complete enrollment by 2016.

13.3 Study Endpoints

13.31 Efficacy Endpoints

Event-free survival: Minimum time to disease progression or recurrence, time to death for any reason, or time to occurrence of a second malignant neoplasm (SMN).

Overall Survival: Time to death from any cause.

Intellectual Competence: Performance is as good as or better than patients treated on CCG 9961 when adjusted for baseline performance

13.33 Analysis of Efficacy

If there are 1 or fewer deaths from tumor progression, within 10 patients, with 3 years median follow up, then a presumption can be made that the reduction in radiation dose has not led to a decline in efficacy. The information would then be supplied to the national group (Children's Oncology Group) as a potential next national Phase III, randomized study.

13.4 Interim Monitoring

13.41 Interim Monitoring of Treatment Efficacy

Because of the short duration of this study, therapeutic efficacy as measured by either EFS or survival, will not be subject to interim monitoring. The first formal analysis of this study will occur when median follow-up is approximately 18 months. The formal early monitoring of dose limiting toxicities and any toxic deaths will provide early warning of significant safety problems.

Because we expect a survival of approximately 90%, if there is one failure in ten patients, we will accept that as equivalent. If there are 2 deaths from tumor progression within the first 10 patients, the study will be closed. All patients will subsequently be monitored. If there are no further deaths and the number of patients is still less than 10, the study will be re-opened to accumulate a total of 10 patients. The expectation is that there will be no toxic deaths. Any toxic deaths will result in the suspension of the study, investigation into the cause of death, and discussion with the IRB.

13.5 Gender and Ethnic Origin

There is no compelling evidence to suggest that outcome of treatment for brain tumors in children is dependent on gender or ethnicity. Hence, the study size will not be powered to detect differences in outcome in groups defined by ethnicity or gender. Therapeutic outcomes will nevertheless be compared among gender and ethnicity categories.

14.0 ADVERSE EVENT REPORTING REQUIREMENTS AND TOXICITY CRITERIA

14.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies, as well as those who will enroll in future studies using similar agents. Adverse events are reported in a defined manner at scheduled and emergent times during a trial, based on occurrence and severity.

14.2 Reporting Requirements

In this study a serious adverse event (SAE) includes death, life-threatening, hospitalization or prolongation of hospitalization, congenital anomaly/birth defects, and persistent and/or significant disability.

Any adverse event that is unexpected and related or possibly related to the study treatment or other research intervention will be reported. Any adverse event that is unrelated to the research intervention does not have to be reported to the COMIRB.

The principal investigator will, within 24 hours, or recognition of any grade 4, non-hematologic SAE that is likely due to radiation, vincristine, or carboplatin, contact the COMIRB.

Death due to disease will be reported if the death occurs within 30 days of the study treatment. All deaths that are possibly related to the study treatment that occur more than 30 days after the treatment will be reported immediately. All other deaths that are due to disease (and therefore expected) and unrelated to the treatment, will be reported at continuing review.

14.3 Toxicity Criteria

Any patient experiencing a non-hematologic, irreversible grade 3 toxicity or grade 4 toxicity should not receive further Carboplatin. The site, measure and grade for all toxicities (Grade 3 and 4) will be according to the NCI Common Terminology Criteria v. 3.0 (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.cancer.gov)

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Appendix 1: Neurological Exam Guidelines

(Within normal limits)

Head Tilt: (Absent)
Visual Acuity: (Intact)
EOMI: (PERRLA)
Cranial Nerves VII - XII: (Intact)
Extremities: (Power, sensation, tone equal bilaterally)
Gait: (WNL)
Dysmetria: (No)
Speech: (Clear)
Memory: (Intact)
Sensory: **(**Normal)

Appendix 2

Karnofsky/Lansky Performance Scales

Karnofsky (Age at least16 years)		Lansky (Age less than 16 years)	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

Appendix 3

NEUROPSYCHOLOGICAL TESTING

Baseline assessment (to be completed by 3-6 months post radiation

age appropriate Wechsler Test
Wide Range Assessment Test-3rd edition
Vineland Adaptive Behavior Scales – Interview Edition
Hollingshead 4 factor Index of Social Position
Achenbach Child Behavior Checklist
Neurologic Status Questionnaire

2 years post- study entrance and 5 years post-study entrance

age appropriate Wechsler Test
Wide Range Assessment Test-3rd edition
Vineland Adaptive Behavior Scales – Interview Edition
Hollingshead 4 factor Index of Social Position
Achenbach Child Behavior Checklist
Woodcock Johnson –Revised; Passage Comprehension
Beery Test of Visual Motor Integration
Neurologic Status Questionnaire