

PBTC-001 Abstract for Health Professionals

Study Title: Pilot Study of Systemic and Intrathecal Chemotherapy followed by Conformal Radiation for Infants with Embryonal Intracranial Central Nervous System Tumors, A Pediatric Brain Tumor Consortium Protocol

Description:

This is a risk adapted, multi-modality trial for newly diagnosed patients under the age of 3 with medulloblastoma/PNET, metastatic ependymoma or other primary intracranial embryonal tumors. It is a collaborative study of the Pediatric Brain Tumor Consortium.

Following surgery, all eligible patients receive 24 weeks of induction chemotherapy consisting of vincristine, cisplatin, cyclophosphamide, oral etoposide and intrathecal mafosfamide.

After induction, patients with no metastatic disease at diagnosis (M0) proceed to local conformal irradiation therapy. Following local irradiation, an additional 12 weeks of adjuvant vincristine, cyclophosphamide, and oral etoposide chemotherapy are given.

Patients with metastatic disease at diagnosis (M+) will receive the same induction chemotherapy noted above. Suggested further non-protocol therapy for this group of M+ patients includes consolidation chemotherapy with high dose busulfan and thiotepea and autologous bone marrow or peripheral stem cell rescue. While this group of patients does require radiation therapy, the recommended doses are based on age and response to consolidation chemotherapy.

Objectives:

1. To evaluate the safety and feasibility of a limited dose escalation schedule of intrathecal (IT) mafosfamide in children < 3 years of age.
2. To evaluate the feasibility, including expected disease progression, of delivering 20 weeks of systemic chemotherapy plus IT mafosfamide.
3. To estimate the subsequent progression free survival and pattern of failure associated with the use of IT mafosfamide and conformal irradiation to the local tumor region followed by 2 further cycles of systemic chemotherapy among patients with initially local disease (M0) at diagnosis.
4. To develop preliminary estimates of the local and neuraxis response rate to intensive postoperative systemic/regional chemotherapy.
5. To document the acute and chronic toxicities associated with the delivery of the first 20 weeks of systemic/regional chemotherapy.
6. To estimate if the first 10 weeks of systemic chemotherapy can restore normal CSF flow, thus permitting administration of intrathecal mafosfamide during the second 10 weeks of systemic chemotherapy in patients initially ineligible to receive intrathecal mafosfamide because of subarachnoid block by tumor.
7. To evaluate the pharmacokinetics of IT mafosfamide using a limited sampling strategy.

Rationale:

The prognosis for children under the age of 3 with embryonal neoplasms is considerably poorer than for older children with embryonal neoplasms. Among the factors that are responsible for the poorer outcome of these patients are an increased incidence of neuraxis dissemination at diagnosis and relapse.

The propensity for widespread neuraxis dissemination mandates the use of craniospinal irradiation as a component of therapy. While such a therapy is an effective and conventional part of therapy for older children, it is associated with an unacceptable high incidence of neuropsychologic sequelae in young children and infants. Current treatment strategies for infants and young children rely on postoperative combination chemotherapy regimens that are intended to at least delay the need of irradiation, potentially diminishing the age associated risk of developmental delays and intellectual deficits in these young patients.

Intrathecal Therapy

At least 30 percent of the patients treated on this protocol are expected to have leptomeningeal disease at diagnosis or relapse. The pre-activated cyclophosphamide derivative, mafosfamide, has shown some activity when given intrathecally. To maximize drug exposure throughout the neuraxis, mafosfamide administration will be alternated between the lumbar and ventricular space.

Systemic Chemotherapy

Cisplatin, cyclophosphamide, and vincristine are known to be active against embryonal CNS tumors. Oral etoposide has shown remarkable efficacy with minimal toxicity. The combined use of these four agents at conventional doses should reduce the likelihood of drug resistance while attempting to minimize hematologic toxicities.

Craniospinal Irradiation Therapy

Craniospinal irradiation (CSI) therapy is the standard treatment in older patients. With the use of adjuvant or consolidation chemotherapy, reduced dose, age-adjusted CSI will be utilized to lessen the associated neurocognitive problems.

Conformal Irradiation Therapy

Conformal or 3D-irradiation therapy uses multiple beams designed to focus the maximum amount of radiation on tumor tissue while sparing adjacent normal brain. This technique is used to deliver local radiation in young patients. It is also used as a boost to the primary tumor site or metastatic sites in patients receiving CSI.

Adjuvant Chemotherapy in MO Patients

There is evidence to suggest that effective chemotherapy with the use of only local rather than craniospinal irradiation may be sufficient treatment in this group of patients. The use of local conformal irradiation should reduce the acute and long term toxicities associated CSI at a young age

Off- Study Recommended High Dose Chemotherapy in M+ Patients

In attempts to reduce the significant incidence of disease recurrence in these high risk patients, high dose busulfan and thiotepa will be used as post induction consolidation chemotherapy. These agents are known to be effective in treating recurrent disease and will be used as treatment in patients with progressive disease during induction therapy. Peripheral blood stem cell support or autologous bone marrow transplant will ameliorate the toxicities.

Eligibility:

- Age < 3 years at time of diagnosis
- Confirmed diagnosis of medulloblastoma, PNET, other embryonal tumor (medulloepithelioma, ependymblastoma, neuroblastoma, pineoblastoma), atypical teratoid/rhabdoid, intracranial germ cell tumor, choroid plexus carcinoma, or M+ ependymoma.
- No previous radiotherapy or chemotherapy other than corticosteroid
- Patients must begin protocol within 35 days of definitive surgery

- Negative bone scan or positive bone scan with bone marrow aspirate/biopsy free of tumor
- No evidence of uncontrolled hydrocephalus or compartmentalization of CSF flow and willing to have an Ommaya reservoir (if not VP or VA shunt) OR if there is evidence of CSF compartmentalization be willing to be re-evaluated after 10 weeks and have an Ommaya placed for IT mafosfamide.
- Performance status: Karnofsky or Lansky $\geq 30\%$
- Bone marrow function:
 - Hgb ≥ 10 g/dl
 - ANC $\geq 1,500/\text{mm}^3$
 - Platelets $\geq 100,000/\text{mm}^3$
- Organ function:
 - Total bilirubin < 1.5 mg/dl
 - SGPT $< 5x$ normal
 - Creatinine normal for age or technetium clearance $\geq 40/\text{ml}/\text{min}/\text{m}^2$
- Willing to have a central line
- Informed consent explained to and signed by patient/legal guardian

Contact:

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