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Infantile Brain Tumors

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Brain tumors are the second most common type of malignancy in children less than 2 years of age. Furthermore, brain tumors as a whole are the most common solid tumor of childhood and 12-15% of all childhood brain tumors occur in children less than two. Childhood brain tumors occur in males more frequently than in females with a 2:1 ratio. The reason for this sex predilection is unknown. Once diagnosed, the treatment of brain tumors in this age group presents many difficult challenges owing to the nature of the developing brain.

Approximately 70% of brain tumors in children under 2 years of age are made up of 3 distinct types: medulloblastoma, ependymoma, and low-grade gliomas. Less commonly, infants may be diagnosed with teratomas (mature or immature) or atypical teratoid-rhabdoid tumor. Medulloblastoma always occurs in the lower compartment (posterior fossa) of the brain but ependymoma and glioma can occur in either the upper or the lower compartments. Overall, 60-70% of infantile brain tumors arise in the upper (supratentorial) compartment.

Posterior fossa tumors can disrupt the flow of the cerebral spinal fluid (CSF) that baths the brain and spinal cord. This can lead to a build up of pressure in the head, which causes nausea, vomiting, headache, and lethargy. In the infantile group, these symptoms often present as persistent vomiting, lethargy, irritability, loss of upgaze, failure to adequately gain weight, and loss of developmental milestones. In the youngest of patients, in whom the bones of the skull have not yet fused, disproportionate head growth and a bulging fontanelle can be signs of increased intracranial pressure. Less commonly, infants will present with seizures or focal findings of weakness in the face, eye muscles or extremities. In some cases, extremity weakness can appear as a rapidly developing hand preference. Many infants present with non-specific

findings which are attributed to more common maladies. Therefore, these patients are often treated for infectious or gastrointestinal diagnoses prior to the discovery of their brain tumor.

Historically, brain tumors in children were treated by surgical removal and, for those tumors with a propensity toward recurrence with metastatic potential, cranial and spinal irradiation. Radiation therapy directed to the developing supratentorial brain has profound negative effects including neuro-cognitive deficits and hypopituitarism; a hormonal deficiency that can result in growth failure, hypothyroidism, failure of sexual maturation, inability to respond to physical stresses and electrolyte imbalances. The severity of these sequelae is inversely proportional to the developmental maturity of the brain. In the current era, it is considered non-standard care to give craiospinal radiation to a newly diagnosed child less than 3 years of age. Therefore, current treatment approaches strive to use chemotherapy to delay or eliminate the need for radiotherapy in this group.

The treatment of brain tumors with chemotherapy is complicated by the presence of the blood brain barrier (BBB). The BBB normally functions to protect the brain from toxins and infectious agents in the bloodstream. A functional BBB also prevents the effective passage of chemotherapeutic agents from the blood into the brain tumor. In the areas immediately adjacent to the brain tumor, the BBB is often porous due to the blood vessel recruitment activity of the tumor. However, the BBB is still able to impede the optimal exposure of all brain tumor cells to systemically infused chemotherapy. Two methods have been developed to overcome this difficulty, high dose chemotherapy with stem cell rescue and intrathecal administration of chemotherapy. Increasing the dose of systemically administered chemotherapy in order to overwhelm the BBB, and achieve higher levels in the brain tumor, is limited by toxicity to the blood forming cells of the bone marrow. This toxicity presents risks for bleeding, anemia, and infection. Blood forming stem cells, harvested from the peripheral blood, stored and infused after the chemotherapy, reconstitute the bone marrow and ameliorate the dose limiting toxicity of high dose chemotherapy. The second approach, intrathecal administration, involves instilling the chemotherapeutic agent through the BBB directly into the cerebral spinal fluid using a surgically placed reservoir. Intrathecal chemo administration of chemotherapy for brain tumors remains the subject of clinical research trials while peripheral blood stem cell rescue after high dose chemotherapy has become a standard therapy at most major medical centers.. Both of these

approaches are most effective for patients with minimal disease remaining after surgery and the first courses of conventionally delivered chemotherapy.

Although these techniques have resulted in long term control of brain tumors without radiation in some patients, chemotherapy alone can not induce durable responses in a significant proportion of patients. In many cases, the use limited field irradiation is considered to help prevent local recurrences. 3-D conformal radiotherapy is one way in which this can be done. 3-D conformal radiotherapy attempts to minimize toxicity by integrating many beams, precisely directing radiotherapy to the desired site while leaving untargeted areas minimally exposed. Intensity Modulated Radiotherapy (IMRT) is a specific conformal technique in which each of the individual beams are shaped in respect to their energy in order to more tightly focus the treatment area and better avoid sensitive normal brain structures. Another emerging technique for focusing radiation is proton beam irradiation. Proton beams have an energy signature that rapidly drops off as a function of the distance traveled; allowing for planning that spares sensitive tissue on the far side of the treatment target. Depending on the tumor size and location, these techniques can offer an advantage in delivering focused radiation to the young child.

In general, chemotherapy can make it possible to delay, decrease or eliminate the radiation normally given to the entire brain and spine in an attempt to prevent relapse distant from the site of the primary tumor. The success of these chemotherapy delivery techniques in decreasing neuropsychological sequelae while delivering effective therapy remains an area of investigation but appears promising.

The treatment of pediatric brain tumors continues to be a very challenging endeavor and all too often, the therapy induces unwelcome long-term side effects. This is especially true in young children due in part to the unacceptable neuropsychological effects of radiation on the developing cortical brain. It is hoped that chemotherapy, administered in novel ways, can reduce, delay or, in some special circumstances, remove radiotherapy from the treatment of brain tumors in the very young.

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