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Aggressive Infantile Embryonal Tumors

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Abstract

Embryonal tumors are the most common brain tumors in infants less than 36 months of age. Histologically characterized as undifferentiated small round cell tumors with divergent patterns of differentiation, these include medulloblastoma, the most common form of embryonal tumor, as well as supratentorial primitive neuroectodermal tumor, medulloepithelioma, ependymblastoma, medullomyoblastoma, melanotic medulloblastoma, and atypical teratoid/rhabdoid tumor. All are similarly aggressive and have a tendency to disseminate throughout the central nervous system. Because of efforts to avoid craniospinal irradiation in an attempt to lessen treatment-related neurotoxicity, management of these tumors in infants is unique. Outcomes remain similarly poor among all the tumor types and, therefore, identification of specific molecular targets that have prognostic and therapeutic implications is crucial. The molecular and clinical aspects of the three most common aggressive infantile embryonal tumors, medulloblastoma, supratentorial primitive neuroectodermal tumor, and atypical teratoid/rhabdoid tumor, are the focus of this review.

Introduction

Embryonal tumors are the most common central nervous system neoplasms in infants less than 36 months of age and are described in the World Health Organization classification scheme as undifferentiated small round cell tumors with divergent patterns of differentiation.¹ Tumors within this classification include medulloblastoma, the most common form of embryonal tumor, as well as supratentorial primitive neuroectodermal tumor, medulloepithelioma, ependymblastoma, medullomyoblastoma, and melanotic medulloblastoma.¹ The atypical teratoid/rhabdoid tumor, which predominantly occurs in infants, had been viewed as a type of medulloblastoma or primitive neuroectodermal tumor, but is now recognized as a molecularly distinct embryonal tumor.¹ Despite sharing common light microscopy features, embryonal tumors appear to evolve by divergent genetic pathways.² Whether the molecular alterations described in embryonal tumors of older children are consistent in infants remains to be confirmed. All of the infantile embryonal tumors are similarly aggressive and have a proclivity to disseminate throughout the central nervous system early in the course of illness.

The principles of management for infantile central nervous system embryonal tumors are unique because therapeutic alternatives to craniospinal irradiation, the mainstay treatment for both local and distant disease control in older children, are currently under investigation in an attempt to lessen treatment-related neurotoxicity. Outcomes remain similarly poor among all the infantile embryonal tumor types and, therefore, identification of specific

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molecular targets that have prognostic and therapeutic implications is crucial. The molecular and clinical aspects of the three most common aggressive infantile embryonal tumors, medulloblastoma, supratentorial primitive neuroectodermal tumor, and atypical teratoid/rhabdoid tumor, are the focus of this review.

Medulloblastoma

Medulloblastoma is the most common malignant brain tumor of infancy and comprises approximately 20% of all primary central nervous system tumors occurring in patients less than 18 years of age.³ Medulloblastoma is believed to arise from the precursor cells of the external granule layer of the developing cerebellum and is predominantly composed of densely packed cells with round to oval hyperchromatic nuclei with generally abundant mitotic activity.¹

The etiologies of infant medulloblastoma are unknown for most patients. There have not been conclusive links between parental occupations or exposures in the development of medulloblastoma, although in some studies parental pesticide use, occupational contact with hydrocarbons and metals, and exposure to N-nitroso compounds have been linked with a higher likelihood of development of medulloblastoma.^{4,5} Several familial cancer syndromes predispose to an increase in risk of developing medulloblastoma in infancy, including *TP53* germline mutation syndromes (Li-Fraumeni), *PTCH* mutations resulting in the nevoid basal cell carcinoma syndrome (Gorlin's), and *APC* mutations characterized in Turcot's syndrome.⁶

In the current World Health Organization classification, medulloblastoma has been histologically divided into two subsets, classic and desmoplastic.¹ Classic medulloblastoma is more frequent, and within that grouping, an anaplastic phenotype that seems to overlap with a large-cell variant has received increasing attention (Figure 1).⁷ Retrospective studies have suggested that the large cell/anaplastic variant may carry a poorer prognosis.⁸ Desmoplastic medulloblastoma, which appears to be less frequently encountered in the infant population, may be associated with a somewhat better prognosis.⁹

Molecular biology

Medulloblastoma is thought to arise from transformed granule cell precursors in the developing cerebellum.¹⁰ Under normal development, granule cell precursors undergo massive proliferation in the external granule layer upon receiving the Sonic hedgehog signal from the Purkinje cell. Granule cell precursors then exit the cell cycle and begin to differentiate and migrate downward to form the internal granule layer. Dysregulated granule cell development, including excessive signals for granule cell precursors to proliferate or an absence of signals to cease dividing, can result in the formation of medulloblastoma. Expression of the neurotrophin-3 receptor, which regulates proliferation, differentiation, and cell death of granule cell precursors, was the first molecular alteration shown to have clinical significance in embryonal tumors.¹¹ Its expression level in medulloblastoma directly correlates with favorable outcome and may indicate a more differentiated histology.¹²

The nevoid basal cell carcinoma syndrome, which is caused by inherited germline mutations of the *PTCH* gene on chromosome 9q22, accounts for 2% of medulloblastoma. *PTCH* encodes the Sonic hedgehog receptor Patched1, which normally represses Sonic hedgehog signaling.¹³ Sonic hedgehog signaling is initiated when Sonic hedgehog binds to Patched1, which releases Smoothened from Patched1-mediated inhibition, resulting in the activation of the downstream growth-promoting transcription factors GLI1 and MYCN. Studies have shown that somatic mutations of *PTCH* and other members of the Sonic hedgehog pathway that similarly result in constitutive activation of Sonic hedgehog signaling are associated

with 10% to 20% of sporadic medulloblastoma.^{14–17} Medulloblastomas arising from either nevoid basal cell carcinoma syndrome or sporadic Sonic hedgehog pathway mutations are predominantly the desmoplastic variant; however, there is overlap, with 9q22 loss also being seen in some nondesmoplastic tumors.¹⁸ These molecular alterations have potential clinical relevance, since *PTCH*(+/-) heterozygous mice spontaneously develop medulloblastoma, which can be induced to regress with Sonic hedgehog pathway antagonists.^{19,20} Furthermore, inactivation of the Sonic hedgehog target gene *GLI1* has also been shown to significantly reduce medulloblastoma formation in this tumor model.²¹

Approximately 5% to 10% of medulloblastomas demonstrate amplification of the *MYCC* oncogene, which has been associated with the large cell anaplastic variant and poor prognosis.⁹ *MYCC* overexpression is more common, observed in 30% to 50% of tumors, including other histological subtypes of medulloblastoma.²² Similarly, expression of the tyrosine kinase receptor *ERBB2* has been demonstrated in 40% of medulloblastoma, more frequently large cell anaplastic type, and is also an independent poor prognostic indicator.²³ *OTX1* and *OTX2* are transcription factors essential to the developing cerebellum. Amplification of the *OTX2* homeobox gene, whose product can be targeted by retinoids, has been identified in large cell anaplastic type medulloblastoma, suggesting that *OTX2* is potentially another therapeutically susceptible oncogene in medulloblastoma.²⁴ More recently, *OTX1* expression was shown to correlate with desmoplastic medulloblastoma while *OTX2* expression correlated with classic medulloblastoma and *OTX2* protein was detected in nearly 80% of classic medulloblastoma.²⁵ Interestingly, the *OTX2*-negative pediatric tumors were found predominantly in children less than 5 years of age.

Gene expression profiling has also provided some important insight into the biology of embryonal tumors. For example, expression analysis has revealed that approximately 15% of sporadic medulloblastoma have activating mutations in the Wntless (Wnt)/beta-catenin signaling pathway and that these alterations in Wnt can be used to identify a molecularly distinct subset of tumors with a more favorable prognosis.²⁶ Upon Wnt binding to its receptor, Frizzled (FRZ), the APC complex is destabilized, liberating beta-catenin to enter the nucleus and activate downstream transcription factors.

Microarray analysis of metastatic (M+) and non-metastatic (M0) medulloblastoma at the time of diagnosis found the platelet-derived growth factor receptor-beta and members of the Ras/MAP kinase pathways to be significantly up-regulated in the M+ tumors.²⁷ These results suggest that the platelet-derived growth factor receptor-mediated signal pathway may be critical in the control of medulloblastoma metastasis. Microarray profiling also revealed that morphologically identical tumors such as medulloblastoma and supratentorial primitive neuroectodermal tumor could be separated based solely on their specific patterns of gene expression and that desmoplastic medulloblastoma was molecularly distinct from classic medulloblastoma, predominantly due to the differential expression of the Sonic hedgehog pathway.²

Loss of genetic material from the short arm of chromosome 17p is the most common cytogenetic abnormality in medulloblastoma, occurring in 35% to 50% of tumors, most commonly as an isochromosome 17q. The majority of the remaining 17p deletions are confined to distal markers near 17p13.3. Although it remains controversial, more recent studies have indicated that isochromosome 17q is an independent poor prognostic feature and that, in general, infant medulloblastoma tend to be associated with fewer genetic copy number aberrations compared with medulloblastoma in older children and hence may represent a genetically distinct form.²⁸

Many of the molecular studies performed thus far have included a subset of medulloblastoma from infants, primarily as a means to show that specific molecules are markers of prognosis independent of young age and other high-risk clinical factors. However, no study has definitively confirmed that the incidence, distribution, and clinical impact of the molecular alterations described for medulloblastoma thus far are equally representative of the infant population in general. In fact, some evidence suggests, at least in the cases of genetic copy number aberrations and OTX2, that infant medulloblastoma may be molecularly distinct. This has important clinical implications, as the infant group is typically treated with chemotherapy alone or delayed radiation therapy and is perhaps most in need of defining valid markers that predict response to treatment as well as biologic targets for tumor-specific therapeutic intervention.

Presentation and diagnosis

Children classically present with the signs and symptoms of obstruction of cerebrospinal fluid flow and cerebellar dysfunction. Infants with medulloblastoma may present less characteristically and have intermittent vomiting, macrocephaly, and nonspecific signs of ventricular dilatation, including the “sun-setting” sign where there is an inability to elevate the eyes.²⁹

Neuroimaging characteristically discloses a relatively well-defined mass lesion that arises in the inferior medullary velum/roof of the 4th ventricle and grows anteriorly into the 4th ventricle; it can invade the middle cerebellar peduncle or the dorsal brainstem.^{29–33} On magnetic resonance imaging (MRI), medulloblastoma are usually homogeneous with low T1 signal and intermediate (between gray matter and white matter) T2 signal; signal is often isointense to gray matter on fluid-attenuated inversion recovery images and hyperintense on diffusion-weighted images (Figure 2).^{29,30,33} In about 75% of cases, the solid portions of the tumors enhance completely and intensely.^{31,33} MR spectroscopy findings are similar for all the embryonal tumors. In general, these tumors have very high levels of choline and very low or absent N-acetyl-aspartate peak (decreased N-acetyl-aspartate to creatine ratio). High choline levels indicate a high degree of membrane metabolism, which usually takes place in rapidly proliferating malignant tumors. Lactate and lipid peaks can also be identified as a result of metabolic acidosis and tissue breakdown.

Staging

Staging studies are crucial in the evaluation of most embryonal tumors, including medulloblastoma.²⁹ Neuroimaging of the entire neuroaxis coupled with sampling of the cerebrospinal fluid for evidence of tumor dissemination are standard components of medulloblastoma management, since as many as 30% of infant patients will have disseminated disease at the time of diagnosis.^{29,34,35} Subarachnoid dissemination along the spinal cord is most common, although intracranial spread may be present. If possible, to avoid artifacts, patients with presumed medulloblastoma should undergo neuroaxis neuroimaging prior to surgery.³⁶ The management of medulloblastoma is dependent on staging studies and the age of the patient. Infants less than 3 years of age are all considered to be in the high-risk treatment group.^{23,29} Molecular genetic parameters found to be associated with poorer prognosis include increased ERBB2, high MYCC expression, and possibly p53 accumulation.^{23,37–40} Recent work has questioned the utility of any single marker and has suggested that gene profile expression classification based on a multigene model may be more useful.^{2,23} Anaplastic/large-cell variants have been predominantly linked with more extensive and/or disseminated tumors and associated in retrospective series with poorer outcome.^{8,9} The identification of molecular markers that predict outcome has blurred the separations between high-risk and average-risk disease groups that have been traditionally based on clinical parameters and raises the possibility that infants may be

similarly split into differing categories of disease risk.^{23,29,39} However, in every study to date, the single most-predictive clinical factor is extent of disease at the time of diagnosis, as independent of age, patients with disseminated disease fare less well.

Treatment and outcome

With present means of surgery, craniospinal radiotherapy, and chemotherapy, between 75% and 90% of children greater than 3 years of age with nondisseminated medulloblastoma are likely to be survivors 5 years after treatment.^{29,36} In contrast, overall survival for infants remains poor, although some subsets of infants, primarily those with nondisseminated localized disease and favorable molecular genetic markers, have a relatively better prognosis, with survival ranging between 50% and 60% 5 years after diagnosis.⁴¹ Of special concern with regard to the treatment of central nervous system tumors in children under the age of 3 is the immaturity of the central nervous system and its sensitivity to the long-term effects of radiation. Thus the volume and dose that can be safely given without causing extensive neurocognitive and endocrinologic sequelae is limited. It is unclear at present whether outcome is poorer in infants because of the inability to administer effective early radiotherapy or whether the biology of infant medulloblastoma is more aggressive.

Surgery

The extent of surgical resection has been associated with outcome in most series, and patients with subtotal resections, especially biopsies, fare less well than those who have undergone a total or near-total resection.⁴² Approximately 30% of patients will ultimately require a permanent external ventricular drainage.

Radiotherapy

Following surgery, craniospinal radiotherapy remains the single most effective means of treatment for medulloblastoma.^{43–45} In a recently completed study of more than 400 children with nondisseminated medulloblastoma (age, 3 to 21 years) who were treated with 2400 cGy of radiation and chemotherapy, survival was greater than 80% at 3 years.³⁶ However, there is significant reluctance to irradiate very young children, especially those less than 3 years of age, with craniospinal treatment. After craniospinal radiotherapy, children, especially those younger than 7 years of age, will have significant intellectual compromise, related predominantly, but not completely, to whole-brain radiotherapy.^{46,47} Two to 3 years after radiotherapy, full-scale intelligence quotients drop 20 to 30 points and the development of significant endocrinologic sequelae are observed in most patients.^{48–50}

With conformal radiotherapy techniques, more precise tumor delivery is possible and studies are underway to determine whether radiotherapy delivered to the primary tumor site with a 1-cm to 2-cm margin will be adequate for disease control in the infant population. Limiting the volume of local radiotherapy will often spare the cochlea and possibly result in less long-term hearing sequelae.

Chemotherapy

Because of the reluctance to use radiotherapy, especially craniospinal radiation therapy in young children, chemotherapy has been extensively explored in children with medulloblastoma who are younger than 3 years of age, and in some studies in children younger than 6 years.^{51–53} Various multi-agent chemotherapeutic regimens have been used and most have included combinations of an alkylator, platinum agent, and a topoisomerase inhibitor administered intravenously or orally. Outcome with such treatment has been relatively disappointing, resulting in disease control in only 20% to 30% of patients. In some studies, craniospinal and local boost radiotherapy were used after completion of

chemotherapy or when the child reached 3 years of age.⁵⁴ Despite this, overall disease control still remained only in the 30% to 35% range. The majority of children who had long-term benefit had nondisseminated, totally resected disease. Multiple studies are presently underway attempting to improve survival by increasing the intensification of pre-radiation chemotherapy, such as the use of higher doses of chemotherapy supported by peripheral stem cell rescue.^{55,56} Preliminary results using this strategy are encouraging.

In attempts to make chemotherapy even more effective and potentially avoid having to administer radiation or at least limit the radiation volume delivered, other drugs have been added to these multi-agent approaches, including intravenous and intraventricular methotrexate and intraventricular and intralumbar mafosfamide, an activated cyclophosphamide derivative.^{41,57–59} There does seem to be a subset of patients who can be treated with chemotherapy alone, and it is likely that the wider availability and application of molecular genetic markers will, in time, better identify this subset. Table 1 highlights the most recent treatment strategies used for infants with medulloblastoma.

Supratentorial Primitive Neuroectodermal Tumors

Supratentorial primitive neuroectodermal tumors, by definition occurring in the cerebrum or suprasellar region, are composed of undifferentiated or poorly differentiated neuroepithelial cells that may show differentiation along various cell lines.¹ Supratentorial primitive neuroectodermal tumors are infrequent, accounting for approximately 2.5% of childhood brain tumors, with peak incidence in the first 3 years of life. Although morphologically indistinguishable from medulloblastoma, cytogenetic and molecular genetic studies have now demonstrated that supratentorial primitive neuroectodermal tumors are distinct.^{2,60} For example, loss of the tumor suppressor gene *PTEN*, observed in about 30% of medulloblastoma, has not been detected in supratentorial primitive neuroectodermal tumors.⁶¹ As of yet, no study has been reported regarding the molecular characteristics of these tumors in infants with regard to prognosis.

Presentation and diagnosis

Supratentorial primitive neuroectodermal tumors commonly present as focal cortical lesions with associated mass effect. Symptoms prior to diagnosis are usually present for less than 6 months.⁶² Seizures may occur, but not as frequently as focal neurologic deficits and symptoms and signs of increased intracranial pressure.⁶² Infants may present with macrocephaly. Neuroimaging studies usually disclose a large, well-defined mass most often located in the fronto-parietal region; supratentorial primitive neuroectodermal tumors can arise either cortically or in the deep periventricular white matter.⁶³ Hemorrhage, necrosis, calcifications, and cyst formation are common; the tumors may be associated with large cystic areas (Figure 3).

Treatment and outcome

As is the case for medulloblastomas, supratentorial primitive neuroectodermal tumors require staging by cerebrospinal fluid cytology and spine MRI evaluation for the identification of subarachnoid dissemination at the time of diagnosis. In most series, 20% or less of infant patients have disseminated disease at the time of diagnosis.

The degree of surgical resection in series of patients with supratentorial primitive neuroectodermal tumors has varied, and in most series the majority of patients, whether infants or young children, have had subtotal resections.^{62–65} However, the extent of surgical resection has not been shown to correlate with outcome. The presence of leptomeningeal dissemination at the time of diagnosis does portend a poorer rate of survival.

Postsurgical therapy has been similar to that for children with poor-risk medulloblastoma.^{52,54,62–65} Treatment with chemotherapy alone, predominantly evaluated in children younger than 5 years of age at the time of diagnosis, has resulted in a poor rate of survival. Outcome may be somewhat better after the use of higher-dose chemotherapy supported by autologous bone marrow transplantation or peripheral stem cell rescue (Table 1).^{55,56,66}

The overall outcome for children with supratentorial primitive neuroectodermal tumors is relatively poor. After treatment with chemotherapy alone, children younger than 5 years of age have a 30% or less chance of 5-year survival. As is the case for children with medulloblastoma, infants with supratentorial primitive neuroectodermal tumors are at high risk for long-term neurocognitive sequelae. This is not only due to the whole-brain radiation therapy these children are often treated with, but also due to the local effects of the tumor and the need for higher-dose boost radiotherapy to the primary tumor site, which results in the surrounding brain receiving doses of radiotherapy ranging between 4500 cGy and 5500 cGy.

Atypical Teratoid/Rhabdoid Tumors

The atypical teratoid/rhabdoid tumor is an increasingly diagnosed lesion that was first fully characterized in the 1980s.⁶⁷ These lesions are composed of rhabdoid cells that are usually intermixed with variable components of primitive neuroectodermal, mesenchymal, and epithelial cells. The rhabdoid cell is a medium-sized, round to oval cell with distinct borders, an eccentric nucleus, and a prominent nucleolus (Figure 4). The primitive neuroectodermal component of the atypical teratoid/rhabdoid tumor is indistinguishable from cells found in supratentorial primitive neuroectodermal tumors. Unlike medulloblastoma or supratentorial primitive neuroectodermal tumors, atypical teratoid/rhabdoid tumors display a wide range of immunoreactivity on immunohistochemical staining, with clusters of cells usually positive for epithelial membrane antigen and vimentin. There is also frequent reactivity for glial fibrillary acidic protein (GFAP), cytokeratin, and, to a lesser extent, for smooth muscle actin and neurofilament protein.

Molecular biology

Molecular genetic investigations have demonstrated that atypical teratoid/rhabdoid tumors are distinct from other embryonal tumors, in that the vast majority demonstrates monosomy 22 or deletions of chromosome band 22q11. Inactivating deletions or mutations of the tumor suppressor gene *hSNF5/INI-1*, located in the chromosomal region 22q11.2, are now regarded as a crucial step in the molecular pathogenesis of most atypical teratoid/rhabdoid tumors. However, at least 20% of cases do not have genomic alterations of *INI-1*, despite showing loss of immunostaining for the INI-1 protein.⁶⁸ *INI-1* encodes a subunit of the SWI/SNF family of chromatin-remodeling complexes, although its direct tumor suppressor function remains unknown.

Presentation and diagnosis

Atypical teratoid/rhabdoid tumors usually present early in life and may constitute as many as 20% of all embryonal tumors. However, the atypical teratoid/rhabdoid tumors have been reported all throughout childhood and into early adulthood. The clinical presentation of atypical teratoid/rhabdoid tumors is indistinguishable from that of medulloblastomas or supratentorial primitive neuroectodermal tumors. About 50% of atypical teratoid/rhabdoid tumors arise in the posterior fossa, 40% are supratentorial, and the rest are pineal, spinal, or multifocal.⁶⁷ Their location can be intraaxial, extraaxial, or both as they often invade

through the meningeal and ependymal boundaries. Leptomeningeal spread occurs in one-third of cases at presentation.

Radiological features are heterogeneous due to the frequent presence of cystic and necrotic areas, calcifications, and hemorrhage. They are usually hyperdense and enhance intensely. With MRI, T1-weighted images often feature hyperintense foci within the lesion because of the hemorrhagic components (Figure 5).

Treatment and outcome

The management of atypical teratoid/rhabdoid tumors, as is the case with other embryonal tumors, begins with staging. The utility of surgery, radiotherapy, and chemotherapy for children, especially infants with atypical teratoid/rhabdoid tumors, is under active study.⁶⁷ Overall survival rates for children less than 3 years of age treated with surgery and chemotherapy, independent of the type of chemotherapy used, have been poor, with survival occurring in less than 20% of patients at 12 months from diagnosis. Treatment has consisted of chemotherapy regimens used for children with medulloblastoma or supratentorial primitive neuroectodermal tumors. The use of other types of regimens, including those for patients with sarcomas and regimens including high-dose and intrathecal methotrexate, have demonstrated questionable increased efficacy. In general, studies have shown that a variety of chemotherapeutic regimens may result in tumor stabilization and in some cases objective tumor shrinkages, but have not resulted in long-term disease control; especially in patients with disseminated disease at the time of diagnosis or in those with subtotal resections. Older patients who have survived have been treated with extensive resections, radiotherapy (craniospinal and local boost), and chemotherapy.⁶⁹ It is unclear whether the better survival in older patients is due to the more aggressive treatment they received or age-related biologic differences. Because of the poorer survival rates in infants, approaches are now focusing on treatment combining aggressive resection with high-dose chemotherapy using methotrexate and, if possible, peripheral stem cell support.⁷⁰ Table 1 highlights the most recent treatment strategies used for atypical teratoid/rhabdoid tumors.

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Figure 1. Medulloblastoma histopathologic variants include classic (A), with sheets of undifferentiated small round blue cells, desmoplastic (B), with tumor cells clustered in nodules and separated by stroma, and anaplastic (C), with relatively large undifferentiated tumor cells displaying irregular nuclear size and shape.

A **B**

Figure 2. Axial T2 (A) and contrast-enhanced T1 (B) images of a 3-year-old with a medulloblastoma. The tumor arises from the anterior midline cerebellum and fills the 4th ventricle. Tumor displays low T2 signal and near complete enhancement. Surrounding edema is evident.

Figure 3.

Hemorrhagic primitive neuroectodermal tumor of the right frontal lobe in a 4-month-old infant. Axial T2 (A), axial T1 pre-contrast (B), and post-contrast (C) images show a large mass with significant hemorrhagic products (bright T1 signal before contrast and mixed low and bright T2 signal). The nonhemorrhagic more peripheral components enhance mildly (C). There is no surrounding edema. A subdural hematoma is evident on the left.

Figure 4. Atypical teratoid/rhabdoid tumor composed of rhabdoid cells intermixed with variable components of primitive neuroectodermal, mesenchymal, and epithelial cells. The rhabdoid cell (arrow) is a medium-sized, round to oval cell, with distinct borders, an eccentric nucleus, and a prominent nucleolus.

Figure 5.

Axial T2 (A) and contrast-enhanced T1 (B) images of an 8-month-old with a large rhabdoid tumor arising in the posterior right lateral ventricle. The mass shows intense enhancement, and has low T2 signal with small islands of high T2 signal that do not enhance (small cysts or necrotic foci). A metastatic lesion is evident deep to the left anterior insula. Hydrocephalus results from posterior 3rd ventricular compression by the tumor.

Table 1

Recent Treatment Strategies for Infant Embryonal Tumors

	Treatment	5-y EFS (%)	(Ref)
MB	Chemotherapy (vcr/cis/cyclo/vp16 or carbo/ifos/vp16) and delayed RT	32 +/- 5	(54)
	Chemotherapy (vcr/cyclo/carbo/vp16/mtx) and IT mtx	82 +/- 9 (CR) 50 +/- 13 (PR) 33 +/- 14 (M+)	(41)
	Chemotherapy (no mtx) alone, then HDCT + RT if evidence of progression/relapse	29 (CR) 6 (PR) 13 (M+)	(57)
	Chemotherapy (multi-agent) alone	14	(65)
sPNET	Chemotherapy (vcr/cis/cyclo/vp16 or carbo/ifos/vp16) and delayed RT	17 +/- 6	(54)
	Chemotherapy (multi-agent) +/- HD-mtx followed by HDCT and autologous PBSC	39	(70)
	Chemotherapy (multi-agent) alone	14	(65)
ATRT	Chemotherapy (vcr/cis/cyclo/vp16 or carbo/ifos/vp16) and delayed RT	14 +/- 7	(54)

Abbreviations: carbo = carboplatin; CR = complete resection; cyclo = cyclophosphamide; EFS = event-free survival; ifos = ifosfamide; HDCT = high-dose chemotherapy; HD-mtx = high-dose methotrexate; IT = intrathecal; M+ = metastatic disease at diagnosis; mtx = methotrexate; PBSC = peripheral blood stem cell rescue; PR = partial resection; Ref = reference citation; RT = radiotherapy; vcr = vincristine; vp16 = etoposide.