Tumor Markers in Infancy and Childhood

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In Brief

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Author Disclosure

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Tumor markers are substances found in abnormal amounts in the blood, urine, or tissues that can be used in the diagnosis, staging, treatment, and surveillance of patients who have cancer. The two most common tumor markers in pediatric oncology, α-fetoprotein (AFP) and β-human chorionic gonadotropin (bHCG), can aid in the treatment of children who have either known cancer or genetically predisposed cancer syndromes.

AFP is a glycoprotein normally synthesized by the fetal yolk sac, liver, and intestine that serves as a fetal type of binding protein. Reference values for serum AFP in the neonatal period and infancy up to 2 years of age have been established from normal term babies who did not have additional factors associated with AFP elevation. Especially in the first few postnatal months, the range of values is broad. Initially, AFP has a half-life of less than 1 week; later, the half-life appears to be longer. Elevations of serum AFP can be seen in association with certain nonneoplastic conditions, most commonly in acute liver disease, such as extrahepatic biliary atresia and hepatitis. In addition, hereditary disorders such as ataxia telangiectasia and tyrosinemia can be associated with serum AFP elevation. The use of AFP as a tumor marker is based on its association with epithelial liver tumors (hepatoblastoma and hepatocellular carcinoma) and certain malignant germ cell tumors (yolk sac tumors [also known as endodermal sinus tumors] and embryonal carcinomas).

bHCG is a glycoprotein produced physiologically by the trophoblasts of the placenta to stimulate hormonal production and maintain pregnancy. Aside from pregnancy, only a few nonneoplastic conditions are associated with an elevation in serum bHCG, most commonly, chronic renal insufficiency. The use of bHCG as a tumor marker is based on its association with trophoblastic differentiation in malignant germ cell tumors such as choriocarcinomas and embryonal carcinomas.

Although evidence-based clinical practice guidelines exist for using tumor markers as screening tools for several cancers in adults, most notably, breast and colorectal cancers, such mass screening guidelines do not exist for the pediatric population. Cancer surveillance protocols in pediatrics are limited to patients who have genetic syndromes that predispose to cancer. Beckwith-Wiedemann syndrome, the best described of several overgrowth syndromes that are associated with an increased incidence of childhood cancer, carries about an 8% risk of intra-abdominal cancers in early childhood, most commonly, Wilms tumor and hepatoblastoma. Although surveillance guidelines vary, the general practice is to screen with abdominal/pelvic ultrasonography and serum AFP measurements every 3 to 4 months until age 4 years for hepatoblastoma, with pelvic ultrasonographic imaging continued until age 8 years for Wilms tumor.

Initial diagnostic evaluation of children in whom a malignant germ cell tumor or liver tumor is suspected includes quantitative measurement of serum AFP and bHCG. Liver function tests always should accompany AFP assessment to exclude nonmalignant hepatic diseases that can be associated with elevated AFP concentrations. For a child who has a liver mass, quantification of serum AFP aids in the diagnosis. The most common primary malignant liver

tumor in childhood, hepatoblastoma, is associated with higher AFP values than hepatocellular carcinoma, which is more common in adolescents. Liver metastases from other malignant tumors, such as neuroblastoma, or benign conditions, such as hepatic hemangioma, are not associated with elevated AFP concentrations.

When a young child who has a liver mass is unable to undergo a diagnostic biopsy because of respiratory compromise, abdominal compartment syndrome, or uncorrectable coagulopathy, a markedly elevated serum AFP value is specific enough to allow for hepatoblastoma-directed emergent therapy. Of note, hepatoblastoma accompanied by low AFP values (<100 ng/mL) is associated with the presence of unfavorable small cell undifferentiated histology and a poor prognosis. Also, although hepatocellular carcinoma typically is associated with lower AFP values than hepatoblastoma, a less common fibrolamellar variant of hepatocellular carcinoma secretes high amounts of AFP.

AFP and bHCG measurements from serum, cerebrospinal fluid (CSF), or serous effusions can aid in establishing the diagnosis of germ cell tumors. In certain well-defined clinical settings, elevated tumor markers can allow for the diagnosis of malignant germ cell tumors without the need for histologic confirmation. In mixed germ cell tumors, the presence of elevated serum AFP or bHCG concentrations should elicit a careful, meticulous review of the histology for elements of yolk sac tumor or choriocarcinoma, respectively. In large immature teratomas that lack morphologic evidence of yolk sac tumor, elevated serum AFP values should prompt immunohistochemistry analysis of the tumor for microscopic foci of malignant yolk sac elements.

Because biopsy technique may allow for only a small sampling of an intracranial germ cell tumor, serum and CSF assessment for AFP and bHCG is paramount. A patient who has an intracranial germ cell tumor associated with elevated AFP or bHCG in the serum or CSF should be treated, even in the presence of contradicting histology, for a nongerminomatous germ cell tumor, which has a poorer prognosis than a pure germinoma and, thus, requires more aggressive therapy.

Although the initial concentration of tumor markers at diagnosis has been investigated as a prognostic indicator, a more common trend is to follow tumor marker rate and magnitude of decline as an indicator of response to therapy. Persistence, a secondary increase, or consistent prolongation beyond the estimated half-life of tumor marker serum values may indicate residual or recurrent malignancy. The half-life of AFP is estimated at 7 days and bHCG at 3 days. A transient elevation in AFP may not necessarily herald persistent active tumor; liberation of AFP from dying tumor cells may cause a reversible increase immediately following the initiation of chemotherapy. Liver dysfunction related to therapy also may cause an increase in AFP. In hepatoblastoma, serum AFP values generally normalize within 4 to 6 weeks following a complete surgical resection; persistence of elevated AFP beyond this period warrants careful evaluation for residual or metastatic disease.

Among children who have initially unresectable or metastatic hepatoblastoma at diagnosis in whom primary surgery is delayed, the decline of tumor markers following neoadjuvant chemotherapy before surgical resection has been demonstrated to have prognostic value. An decline of at least 1 log from baseline is associated with improved survival. In malignant nonseminomatous germ cell tumors, AFP and bHCG are excellent tumor markers for monitoring the response to therapy. Tumor marker decline has been evaluated as a potential prognostic marker to guide further therapy in such patients.

Serum tumor marker surveillance is a valuable tool in assessing patients for relapse of malignant germ cell tumors and liver tumors. In general, low-risk patients who are treated with surgery alone are followed more frequently than those who receive adjuvant chemotherapy, with the aim of detecting relapse early to allow timely intervention. A consistent increase in serum tumor markers in some cases can precede a clinically apparent relapse. Most practice guidelines advocate for at least monthly serum tumor marker screening during the first year after therapy, followed by more extended intervals thereafter for approximately 5 years.

Unlike in the adult population, population-wide tumor marker screening of pediatric patients for malignant tumors is not appropriate. Elevations in AFP and bHCG need to be evaluated in clinical context to distinguish malignant from nonmalignant sources. In pediatric oncology practice, these tumor markers aid in the prognosis and treatment of patients who have secreting malignant tumors, most commonly, intracranial and peripheral malignant germ cell tumors and the primary liver tumors hepatoblastoma and hepatocellular carcinoma.

Comment: Urine vanillylmandelic acid and homovanillic acid, metabolites of norepinephrine and dopamine, are tumor markers for neuroblastoma, the most common cancer of infancy and the most common extracranial solid tumor of childhood. Studies in Japan, Great Britain, Germany, and Canada have investigated screening programs, usually at 6 months of age, to detect undiagnosed neuroblastomas. The National Cancer Institute has determined that such screening does not result in decreased mortality. Aside from false-positive results, most tumors identified by mass screening programs are early-stage neuroblastomas, which have a

high likelihood of spontaneous regression. In other words, most of the tumors found would have disappeared without ever becoming symptomatic, but their identification leads to the enormous anxiety associated with cancer and often to treatment that is more likely to be toxic than beneficial. The ability to screen does not mean that all screening should be undertaken, an issue raising controversy for our colleagues in adult medicine about the use, for example, of prostate-specific antigen as a screen for prostate cancer.

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Editor, In Brief

In Brief

Pheochromocytoma

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Author Disclosure

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Pheochromocytoma, a rare disease occurring more often in adults than in children, accounts for only about 1% of pediatric hypertension and often is associated with a variety of genetic syndromes. The National Registry of Childhood Cancers reports an incidence of 0.11 benign and 0.02 malignant pheochromocytomas per 1 million children. Eighty-five percent of pheochromocytomas are located in the adrenal glands; the rest develop in the extra-adrenal parasympathetic and sympathetic paraganglia. Most tumors are less than 5 cm in size, and 25% to 33% are bilateral. Approximately 10% of intra-adrenal and 40% of extra-adrenal pheochromocytomas are malignant. In childhood, these tumors are more prevalent in boys than girls, but during adolescence this trend reverses, possibly because of hormonal influences.

In children 18 years of age and younger, about 60% of pheochromocytomas have an associated germline mutation, and in children younger than 10 years, this number increases to 70%. Familial genetic syndromes predispose to the development of pheochromocytoma by altering sympathetic neuronal cell precursor apoptosis. A family history of genetic syndromes is common but not equivocal in affected children. Many associated syndromes are autosomal dominant, but spontaneous mutations occur.

The Table summarizes four familial syndromes commonly associated with pheochromocytoma. Von Hippel-Lindau syndrome (VHL), a neurocutaneous syndrome associated with 20% of all pheochromocytomas, carries a 10% to 20% risk of developing pheochromocytoma. The tumors can be bilateral or extra-adrenal, but only 5% associated with VHL are malignant.

Multiple endocrine neoplasia (MEN) types IIA and IIB are associated with pheochromocytoma. MEN IIA manifests with parathyroid hyperplasia, adrenal medullary hyperplasia or pheochromocytoma, and medullary thyroid carcinoma. MEN IIB is characterized by neuromas, medullary carcinoma, and pheochromocytoma. The risk of pheochromocytoma in MEN IIA is about 50% and in MEN IIB is higher.

Neurofibromatosis type 1, an autosomal dominant syndrome associated with café au lait macules, Lisch nodules, neurofibromas, optic gliomas, and axillary or inguinal freckling, carries a 1% risk of pheochromocytoma. In familial paraganglioma syndrome, which is also autosomal dominant, paragangliomas develop in the head, neck, chest, abdomen, and pelvis; about 20% of affected patients develop a pheochromocytoma.

Pheochromocytomas become symptomatic from the increased secretion of norepinephrine (predominant in chil-

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