The Impact of Genetic and Biological Alterations in the Management of Pediatric Solid Tumors

Jay L. Grosfeld, M.D.
Indiana University School of Medicine, Indianapolis, Indiana, U.S.A.

During the past 25 years, five-year survival rates for children with cancer have improved from 56% to 75%. While multidisciplinary cooperative group trials and combined cancer therapy have improved survival, more recent concepts of individualized treatment using biologic and genetic risk factors as predictors of outcome have become essential in determining care. Identification of specific genes, oncogenes, tumor markers and other biologic and pathologic factors play an important role in both staging and risk categorization of specific tumors as low, moderate or high risk lesions. Risk based management allows pediatric medical and surgical oncologists to individualize treatment in each patient to maximize survival, minimize morbidity and improve the quality of life.

Although a decrease in cancer incidence and mortality has been observed in adults recent data document an increased incidence of cancer in infants. Boys have an increased rate of CNS tumors, neuroblastoma, and retinoblastoma; whereas girls had an increased rate of teratomas and hepatoblastoma (particulary in very low birth weight infants). Leukemia is the most common pediatric malignancy followed by brain tumors while neuroblastoma is the most common solid abdominal tumor. Wilms’ tumor, soft tissue sarcomas (STS), bone tumors, hepatoblastoma and hepatocarcinoma, teratomas and germ cell tumors are the other more common pediatric solid tumors. Current 5 year survival for Neuroblastoma is 45%. Wilms’ tumors 88%. STS 73%. Hepatoblastoma 65% Hepatocarcinoma <20% and germ-cell tumors 65%.

Genes are intimately involved in cancer induction and progression. Changes in chromosomal number (ploidy), translocation (gene fusion) deletions (loss or inactivation of suppressor genes), gene amplification (oncogenes) and point mutations (chromosomal disruption) are commonly noted. Examples in pediatric tumors include MEN-1 [11q12-13] menin gene; MEN-2 [10q11.2] ret-oncogene; Wilms’ tumor (WT-1 [11p13]; WT-2 [11p15.5]; 16q3; Neuroblastoma 1p36, N-myc oncogene [2p]; 17q. 14q, bel-2, trk-A. NGFR, CD-44, nm-23, GD-2; hepatoblastoma [5q]; rhabdomyosarcoma [11p15]; NF-1 [17q11]; p53 oncogene [17p3]; alveolar type [5(2;13)q35; q14] PAX3-FKHR fusion]; and [t(1;13) (q36; q14) PAX7-FKHR fusion]. Identification of specific gene
alterations is critical in establishing behavior (low vs. high risk) and determining the intensity and type of treatment required.

Future cancer therapy will include variants of gene therapy (gene repair or suicide genes to directly kill tumor cells), interleukins (IL-2; IL-12) and other cytokines to enhance immunotherapy, tumor vaccines, antiangiogenic agents, antiangiogenic antibodies (anti-VEGF), isotopic and molecular target therapy, and combined modalities of targeting, immunotherapy and anti-angiogenesis.