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THEME ARTICLE

An update in pediatric oncology*

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Abstract

Although childhood malignancies are rare, they represent the most common cause of death from disease in children less than 15 years old. Fortunately, the outlook for children with cancer has been improving steadily as newer methods of diagnosis, staging, and treatment are developed.

Introduction

Nearly 30% of adults will develop cancer in their lifetime, but childhood cancer is relatively rare. In 1985, there were only an estimated 6550 new cases of childhood cancer in the United States (Young et al. 1986).

Children differ greatly from adults not only in their incidence of cancer, but also in the types of cancer that they develop. Almost 85% of pediatric malignancies are either hematologic (leukemia or lymphoma), sarcomas, or embryonal tumors (Table 1, top of next page), whereas 85% of adult cancers are carcinomas (Sutow et al. 1984).

Childhood cancer may be relatively rare, but it has considerable impact on the pediatric health care system as the leading cause of death from disease in children less than 15 years old. In 1982, childhood cancer caused 4.3 deaths per 100,000 population. Despite the apparent bleakness of these facts and figures, the death rate from childhood malignancies has been declining steadily and is now only half of what it was in 1950. It is anticipated that nearly 60% of the children diagnosed today with a malignancy will be long-term survivors (Young et al. 1986).

There are multiple reasons for this dramatic improvement in childhood cancer statistics, but most ultimately can be traced to the influence of national collaborative pediatric clinical group studies. Most U.S. children diagnosed with cancer are referred to tertiary care centers where they are evaluated by a multidisciplinary team and then placed on collaborative treatment protocols. These studies, which allow statistically significant numbers of patients to be staged and treated in a consistent, evaluable fashion over a relatively short period of time, have led to a veritable explosion of knowledge, not only concerning the best therapies, but also concerning tumor biology, prognostic indicators, and supportive care techniques.

Advances in Diagnostic and Therapeutic Modalities

Tumor Biology

Collaborative study participation requires histologic central review by a reference pathologist. It was through such reviews of large numbers of patients that certain histologic patterns with prognostic significance have been discerned for several common childhood malignancies, such as Wilms' tumor and rhabdomyosarcoma. Patients with less favorable histologies are given more intensive treatment in an effort to improve historically inferior survival statistics (Favara et al. 1986).

More recently, fresh tissue and serum/plasma samples often are requested to be sent to reference laboratories for cytogenetics, immunophenotyping, immunohistochemical studies, flow cytometry, molecular probes, and/or specific and nonspecific tumor markers. While many of these sophisticated investigations are still in their infancy, several already have yielded valuable prognostic or staging information with obvious therapeutic implications (Dehner 1989).

Prognostic Indicators

Prognostic indicators are a relatively new phenomena, a product of our success in combating childhood cancer; there were no prognostic factors when no one survived their disease. As treatments improved and

* This year the Journal has invited several refereed papers devoted to the medically compromised child. The first of this series is focussed on pediatric oncology.

survival duration increased, it became increasingly apparent that some children did better than others. Analyses of children with acute lymphoblastic leukemia (ALL) provided some of the most extensively studied prognostic indicators (Table 2, bottom of this page).

Our new-found ability to stratify patients into risk groups based on their prognostic factors ensures that the outcome of randomized clinical trials is influenced only by the treatment employed and not by inherent biologic differences in the patients themselves. This stratification also allows therapy to be somewhat individualized—with high-risk patients receiving maximally tolerated therapy, and low-risk patients receiving less intense, and therefore, less toxic treatment. These principles have been applied most extensively to children with Wilms' tumor, but also to certain patients with ALL, rhabdomyosarcoma, neuroblastoma, and lymphoma (Hammond 1986).

Supportive Care

Most chemotherapy is administered intravenously, often by infusion and often accompanied by vigorous hydration. Some of the more commonly used agents are sclerosing, causing tissue necrosis if suffused outside of the vein. These patients also need frequent blood-letting (for monitoring of toxicities) and frequent antibiotic, nutritional, and transfusion support. For all these reasons, it was a major physical and psychological advance when long-term, indwelling catheters were developed. These catheters, inserted surgically, are advanced into the right atrium and terminate distally either by tubing exiting out the chest wall or via a totally implanted subcutaneous reservoir which is accessed with special needles. The major complication associated with these catheters is infection (Mirro et al. 1989). Children with these vascular access devices probably should receive SBE prophylaxis whenever undergoing dental procedures, and the possibility of catheter sepsis always should be considered whenever these patients develop a fever, regardless of their blood counts or immune status.

Newer Therapeutic Concepts

The traditional antineoplastic triad—surgery, radiation, and chemotherapy, remains essentially intact, but the role these modalities now play and their interrelationships have changed in recent years.

The number of pediatric tumors in which the surgeon's ability to totally resect the mass is the most important prognostic factor has been reduced to only a few specific situations such as in liver tumors, soft tissue sarcomas other than rhabdomyosarcoma, and early stage neuroblastomas. In rare circumstances, such as limb-salvage procedures instead of simple amputations, the surgeon may actually perform more extensive surgery, but mutilative surgery has now virtually been abandoned (Hays 1989).

Radiation therapy also seems to be playing a smaller role in the initial management of pediatric malignancies. Prophylactic cranial irradiation largely has been abandoned in many low-risk ALL patients. Likewise, early stage Wilms' tumor and rhabdomyosarcoma patients no longer receive local radiation therapy. In certain other situations, total dose or volume can be reduced in an attempt to lessen the risk of potential late effects (Fryer 1986). A new radiotherapy technique, hyperfractionation, also is under investigation.

Chemotherapy has become the mainstay of treatment in pediatric malignancies and is largely responsible for markedly improved survival statistics. The rate of development of new agents has slowed in the last decade, but improved knowledge of the pharmacology and pharmacokinetics of these agents has resulted in more effective combinations and dosing schedules (Balis et al. 1989).

TABLE 1. Incidence of Major Types of Malignancies in United States Children Less Than 15 Years of Age

Type of Malignancy	*Rate per million per year**	
	White	*Black*
Leukemias	42.1	24.3
Brain tumors	23.9	23.9
Lymphomas	13.2	13.9
Sympathetic nervous system tumors	9.6	7.0
Soft tissue sarcomas	8.4	3.9
Kidney tumors	7.8	7.8
Bone tumors	5.6	4.8

*Data from the Third National Cancer Survey, 1969–71.

TABLE 2. Unfavorable Prognostic Indicators in Childhood Acute Lymphoblastic Leukemia

Hematologic findings:	WBC > 50,000 per mm3 (strongest indicator)
Age:	< 2 years or > 10 years (Infants < 1 year—very poor)
Cytogenetics:	Ph^1 chromosome
	Hypodiploidy or pseudodiploidy
	Translocations
Physical findings:	Mediastinal mass
	Massive hepatosplenomegaly
	CNS leukemia
Immunophenotype:	B-cell > T-cell > pre-B-cell
	cALLa negative
Sex:	Male
Race:	Black

Recently, bone marrow transplantation has become a fourth therapeutic modality in some cases of acute and chronic leukemia, recurrent lymphoma and advanced stage neuroblastoma, and other high-risk solid tumors where conventional therapy offers little hope of long-term survival (Ramsay 1989). Sources of bone marrow may come from identical twins (syngeneic), HLA-identical or near-identical siblings, close relatives, or random donors (allogeneic), or from the patient himself (autologous) during disease remission. In this latter instance, the harvested autologous marrow usually is subjected to a "purging" process to try to rid it of any residual malignant cells.

In the following sections, specific common childhood malignancies will be discussed and the role of the above-mentioned newer diagnostic, staging, and therapeutic modalities will be emphasized.

Pediatric Malignancies

Childhood Leukemia

Leukemias are a heterogeneous group of diseases in childhood and represent approximately one-third of all childhood malignancies. Childhood leukemias have been studied intensely and have served as the model for development of treatment principles for many cancers in both children and adults. These diseases are divided into lymphoid and myeloid types and into "acute" and "chronic" forms to denote the putative cell of origin and the clinical course (prechemotherapy era), respectively. With current therapy the leukemias are not often truly "acute" and the course is usually that of a chronic disease.

Acute lymphoblastic leukemia (ALL) accounts for 75-80% of childhood leukemias and is the most common single malignancy in children. Its peak incidence is between 3 and 5 years, but it may occur at any age. ALL is slightly more common in males and in whites (Miller 1990). Like other leukemias, ALL is the result of a malignant transformation and clonal proliferation of a single cell (Dow 1985). The etiology of the leukemogenic event is unknown, but data suggest that it is multifactorial with potential contributions from genetic (Marks 1981), environmental (Farber 1981), and viral infectious factors (Bishop 1985). Certain groups of patients such as those with chromosomal abnormalities (e.g.: Down's syndrome) and those with certain immunodeficiency states and congenital abnormalities are at increased risk of developing leukemia. Siblings of children with ALL have a fourfold increased risk over the general population, and the concordance rate of ALL in identical twins is approximately 25% in the first 5 years of life (Steinherz 1987).

ALL may present with a variety of signs and symptoms. These are related to the cell mass in the bone marrow and in extramedullary sites. At presentation the child may be completely asymptomatic or (more commonly) have fatigue, bone pain, fever, weight loss, and/or bleeding. On physical examination it is common to find pallor, petechiae, hepatosplenomegaly, lymphadenopathy, and bone tenderness. It is not necessary for the leukocyte count to be elevated at diagnosis, and more than half of patients have an initial leukocyte count $<10,000/mm^3$, with or without blast cells in the peripheral smear. Fewer than 20% have leukocyte counts greater than $50,000/mm^3$ (Steinherz 1987). Anemia usually is present at diagnosis, and thrombocytopenia may be severe, although bleeding other than petechiae and ecchymoses is unusual. The diagnosis is established by the presence of >25% lymphoblasts in the bone marrow, although most patients have >65% lymphoblasts in the marrow.

Classification of lymphoblastic leukemia depends upon data from morphology, cytochemical stains, immunophenotyping, biologic assays, and chromosomal analysis. Monoclonal antibodies directed against lymphocyte differentiation antigens and the common ALL antigen (cALLa) allow the immunophenotyping of ALL into T-cell, B-cell, pre B-cell, and early pre B-cell subtypes having prognostic significance (Miller 1990). Karyotyping of lymphoblasts has become an important tool in studying the biology of acute leukemia and determining more effective therapy. The finding of hyperdiploidy is a favorable prognostic feature, whereas hypodiploidy, pseudodiploidy, or translocations are associated with a higher risk of induction failure or early relapse (Poplack 1989). These laboratory findings, as well as clinical features at diagnosis, are used to predict outcome and to assist in tailoring therapy (Table 2).

The goal of therapy for ALL in children is cure. This has become an achievable goal for most patients and requires the use of multiagent chemotherapy aided by well-planned supportive care. The first step is to achieve remission and this is accomplished in >95% of patients using a 4-week cycle of vincristine, prednisone and L-asparaginase. Consolidation therapy, including therapy aimed at preventing central nervous system (CNS) relapse, is administered to further reduce the leukemic cell burden. Maintenance therapy using long-term, less intensive drug schedules is needed to allow dormant cells to enter the cell cycle and be killed. For patients with standard risk, the use of intrathecal methotrexate for CNS prophylaxis and maintenance with daily oral 6-mercaptopurine and weekly methotrexate, plus pulses of vincristine and prednisone, may be effective therapy. Increased-risk patients must be treated more intensively, and numerous large-scale clinical trials are underway to test and compare different treatment regimens. Treatment generally is continued for 2 1/2 to 3

years, and there is a 15–20% risk of relapse after discontinuation. Overall, the probability of having a long-term (>5 years), event-free survival is approximately 60% (Miller 1990; Steinherz 1987; Poplack 1989).

Bone marrow relapse while on chemotherapy or within six months of discontinuation is an ominous sign, and, with conventional chemotherapy alone, almost all such patients will die of disease. Death usually is the result of infection, bleeding, or both. While second (and even third or fourth) remissions may be achieved, other methods of management, such as bone marrow transplantation, are being investigated for this group of patients. CNS relapse may occur in conjunction with bone marrow relapse or as an isolated event, and relapses also may occur in the testicle, skin, retina, or other extramedullary sites.

Much progress has been made in the management of childhood ALL, but there are numerous problems yet unsolved. Progress is necessary to prevent and treat relapse, find new treatment modalities, and minimize long-term effects of therapy.

Acute nonlymphocytic leukemia (ANLL) makes up about 15–20% of the leukemias occurring in children and shares many of the clinical features seen in ALL. ANLL is the result of a malignant clonal proliferation of a primitive myeloid cell. There is expansion of the malignant population and infiltration of the bone marrow and extramedullary tissues. Normal hematopoiesis is impaired, resulting in anemia, thrombocytopenia, and neutropenia. As in ALL, the child with ANLL may present with pallor, fatigue, infection, bleeding, bone pain, and splenomegaly. Marked lymphadenopathy and hepatomegaly are not common. Uncommonly, the patient may present with a solid tumor mass (chloroma), gingival hyperplasia and infiltration (with monoblastic or myelomonoblastic types), or disseminated intravascular coagulation with a severe bleeding diathesis (associated with acute promyelocytic type) (Hakami and Monzon 1987).

The French-American-British (FAB) classification defines seven types of ANLL (M_1–M_7) based on morphologic criteria of the direction and degree of myeloid differentiation expressed (Bennett et al. 1976; 1985). Chromosomal abnormalities of the leukemic cell population are commonly found, but their prognostic significance is not yet determined. Immunophenotyping of cell surface markers in ANLL also is in a somewhat earlier state of development than that of ALL (Grier and Weinstein 1989).

Management of the child with ANLL is similar to that employed with ALL, including the need for aggressive remission induction therapy, intensive supportive care, and CNS prophylaxis. Remission induction therapy is used to induce a state of bone marrow ablation. During this period of aplasia, infectious complications and bleeding may result in 15–20% mortality; therefore, prompt and intensive supportive care is essential (Hakami and Monzon 1987). Remission rates in children approach 75–85%. CNS relapse may occur, and it is necessary to give CNS prophylaxis (Grier and Weinstein 1989). The role of maintenance therapy in ANLL is uncertain, since regimens used thus far have not resulted in the same type of prolonged remissions seen in ALL. It is more likely that shorter courses of intensive postinduction chemotherapy may result in more durable remissions. Five-year, event-free survival of 25–45% is reported with conventional chemotherapy, and rates of 60% are reported with allogeneic bone marrow transplantation (Grier and Weinstein 1989). In those patients lacking an allogeneic donor the role of autologous marrow transplantation is being investigated.

Chronic myelocytic leukemia (CML) is rare in childhood, accounting for fewer than 5% of all leukemias. This malignant clonal panmyelopathy involves all of the hematopoietic cell lines and often some lymphoid lineages as well (Altman 1989). The "adult" form of CML, which also is the most common type in childhood, is associated with the Philadelphia chromosome (Ph^1) as a specific cytogenetic marker of the malignant clone. A "juvenile" form of the disease (JCML) lacks Ph^1 and often is a more rapidly progressive disease, occurring in children younger than two years of age and demonstrating marked resistance to drug therapy. Bone marrow transplantation has been effective in controlling JCML. Adult type CML in children shares many of the features seen in adults and is characterized by myeloid hyperplasia of the bone marrow, extramedullary hematopoiesis, and extreme leukocytosis with the full range of granulocyte precursors in the peripheral blood. The leukocyte count may be controlled for long periods of time by busulfan or hydroxyurea, but the disease ultimately undergoes blast transformation with development of a drug-resistant blast population and ultimate death of the patient. Bone marrow transplantation in chronic phase of the disease offers the only real hope of long-term control.

Lymphomas

Malignant lymphomas make up approximately 10% of all childhood cancer, with Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) accounting for approximately equal numbers of cases. The lymphomas will be presented as separate entities in this discussion.

Hodgkin's disease is a malignant disease of the lymphoreticular system characterized histologically by infiltration of involved organs by Reed-Sternberg cells and varying degrees of lymphocytic proliferation and structural-supportive cells (Miller 1990). Both the etiology of HD and the cellular origin of the pathognomonic

Reed-Sternberg cells remain unknown, but epidemiologic, immunologic, and pathologic features of the disease have been described in detail (Sullivan 1987; Leventhal and Donaldson 1989; Miller 1990). Thirty per cent of all cases occur before age 20 with more than half of these in the 15–19 year age group. In children there is a male to female ratio of 1.8 (Miller 1990). Patients often are anergic at diagnosis, and there is commonly an abnormal pattern of cellular immunity which may persist despite successful treatment for the disease (Leventhal and Donaldson 1989).

HD is classified histopathologically by the degree of lymphocytic proliferation and supporting cells. Four pathologic types of HD are recognized:

1. Nodular sclerosing (about 50% of cases, favorable prognosis)
2. Lymphocyte predominant (18% of cases, most favorable)
3. Mixed cellularity (28% of cases, guarded)
4. Lymphocyte depletion (2% of cases, least favorable).

Generally, there is an inverse relationship between the number of Reed-Sternberg cells and the degree of lymphocyte proliferation (Miller 1990).

The clinical features of HD in children are similar to those seen in adults. Nonspecific constitutional symptoms include: fever, weight loss, anorexia, cachexia, diaphoresis, and pruritis. The findings of persistent fever, night sweats, and loss of more than 10% of body weight in the 6 months preceding diagnosis are important staging criteria in the commonly employed Ann Arbor clinical staging system. Enlarged, nontender lymph nodes occurring in the cervical (49%) or supraclavicular and mediastinal (38%) areas often are the presenting findings. Mediastinal HD is seen in more than half of surgically staged patients and often is seen in teenagers and young women having nodular sclerosing disease (Miller 1990). The disease also may involve lung parenchyma, liver, spleen, bones, bone marrow, or retroperitoneal nodes. Routine clinical laboratory investigations are too nonspecific to be very helpful in the diagnosis of HD, but are useful in excluding other potential etiologies for presenting signs and symptoms. Excisional biopsy of involved lymph nodes is essential for diagnosis, and bone marrow biopsy is required. Radiographic imaging studies should include plain radiographs of chest and areas of suspected bony disease; CT scans of chest, abdomen, and pelvis; bone scan; and (possibly) bipedal lymphangiography.

Staging makes it possible to tailor therapy to the extent of disease, since it is known that HD generally progresses in a stepwise manner from one nodal group to the adjacent group. The Ann Arbor staging classification defines four groups (I-IV) and assigns each an "A" or "B" designation, depending upon the presence or absence of fever, weight loss, and/or night sweats. About two-thirds of pediatric patients will have Stage I or II disease at diagnosis, and about 25% will have "B" symptoms (Leventhal and Donaldson 1989). Staging should include laparotomy and splenectomy, unless the patient is proved to have Stage III or IV disease by nonsurgical methods.

HD therapy is determined by stage and may involve radiation therapy alone (Stages I and II-A), chemotherapy alone (Stages III-B and IV), or a combination of both modalities (Stages II-B and III-A). The technique of radiation therapy for HD still is undergoing modification, especially for the pediatric age group. Chemotherapy also is not standardized, although the 4-drug combination MOPP (procarbazine, prednisone, vincristine, and nitrogen mustard) with or without the combination of ABVD (doxorubicin, bleomycin, vinblastine, and DTIC) has proven to be effective in most patients. Results of therapy vary widely, but 5-year, event-free survival for Stage I disease is about 95%, and even in Stage IV it may approach 75% (Miller 1990).

Non-Hodgkin's lymphomas (NHL) are malignant neoplasms of the constituent cells of the immune system and in children almost always are widespread diseases at the outset. These diseases differ from HD in the extent of disease at diagnosis, rate and manner of tumor progression, incidence of leukemic conversion (i.e., bone marrow infiltration), CNS involvement, and response to radiation and chemotherapy. NHL accounts for about 4% of all cases of cancer in children, has a relatively constant age incidence throughout childhood, and occurs three to four times more commonly in boys than girls. While the etiology of NHL remains unknown, there are data suggesting a viral role. The Epstein-Barr virus (EBV) is linked epidemiologically to the African (endemic) form of Burkitt lymphoma (but not to the American or sporadic form); large cell lymphomas have occurred more frequently in persons infected with the human immunodeficiency virus (HIV); and adult T-cell leukemia/lymphoma definitively has been linked to HTLV-I (Miller 1990).

The classification of NHL has been extremely complex, but the Rappaport classification system currently in use is practical for childhood NHL, and correlation of this system with immunologic cell markers makes the heterogeneity of NHL more understandable. Nodular (or follicular) NHL is extremely rare in children; therefore, for practical purposes, childhood NHL has a diffuse pattern with complete effacement of involved normal tissues. Three major subgroups are seen:

1. large cell or histiocytic (16% of cases)
2. lymphoblastic (33%)
3. undifferentiated lymphomas (47%).

The large cell type may have different histologic patterns and generally is of B-cell origin. The lymphoblastic type almost always is of T-cell origin, and the undifferentiated types are B-cell neoplasms (Link 1985; Miller 1990).

NHL may arise in virtually any site of lymphoid tissue and numerous extralymphoid sites, such as bone, skin, and the orbits (Murphy 1980). Painless lymphadenopathy is common at diagnosis, as are the nonspecific constitutional symptoms of weight loss, anorexia, fever, and malaise. Other symptoms are related to specific sites of disease such as the abdomen where pain, ascites, abdominal mass, intestinal obstruction, intussusception, and hepatic involvement may herald a Burkitt lymphoma. Mediastinal involvement often is seen with lymphoblastic disease; it may be massive and associated with respiratory symptoms, superior vena cava syndrome (plethora, facial edema, cyanosis, and distended neck veins), pleural effusion, and striking cervical and supraclavicular adenopathy. Bone marrow involvement often is seen in lymphoblastic disease, and the degree of marrow infiltration may make the difference between describing the disease as lymphoma or acute lymphoblastic leukemia (T-cell ALL). An arbitrary figure of 25% blast cells in the marrow often is the criterion for this distinction, and the diseases are treated similarly. CNS involvement frequently is seen in both lymphoblastic and Burkitt lymphoma (Miller 1990).

Clinical investigation of NHL generally should include bone marrow aspiration/biopsy, cerebrospinal fluid examination, and radiographic studies, including chest radiographs, CT scan of chest and/or abdomen, bone scan, and (possibly) gallium scanning. These procedures are necessary to properly stage the patient's disease in order to plan appropriate therapy. Lymphangiography is not helpful, and staging laparotomy with splenectomy is not indicated. A variety of staging systems are in use, with the St. Jude system (Murphy 1980) most widely used at present.

Discussion of NHL therapy is beyond the scope of this paper, but in virtually all cases involves the use of intensive multiagent chemotherapeutic regimens, with or without radiation therapy to the CNS or to sites of bulky disease. Successful therapy depends upon a strategic approach similar to that used in childhood acute lymphoblastic leukemia and includes accurate staging, histopathologic classification, multidrug induction, intensification, and maintenance regimens, with CNS prophylaxis and aggressive supportive care. Considerable success in treating lymphoblastic lymphoma and Burkitt lymphoma has been realized, with long-term, event-free survival approaching 70–80% and 75%, respectively (Magrath 1987).

Tumors of the Central Nervous System

Primary tumors of the CNS account for 17–20% of all childhood cancer. In childhood and early adolescence CNS neoplasms of embryonal origin predominate while later there is an increase of adult-type gliomas. This suggests that the occurrence of these tumors is not random and that children may have CNS tumors of distinctly different etiology (Heideman et al. 1989). Unlike adults, children have few malignant diseases metastatic to the brain, and intracranial masses usually are primary CNS tumors.

The diagnosis of CNS tumors was revolutionized by the development of computed tomography (CT) scanning which can detect more than 95% of tumors. Diagnostic capabilities are even further enhanced by the addition of MRI scanning and the (as yet) limited availability of positron-emission tomography (PET) and single-photon emission computed tomography (SPECT). These noninvasive procedures generally have replaced pneumoencephalography, nuclear medicine scanning and, to a large extent, selective cerebral angiography and ultrasonography as the diagnostic tools available to the clinician. Gadolinium-enhanced MRI likely will have an expanded role in neuro-imaging, since it allows superior delineation of infiltrating tumors (Finlay 1987).

The child with a brain tumor is likely to present with the nonspecific and nonlocalizing findings of increased intracranial pressure (ICP), often resulting from obstruction of the fourth ventricle. There may be resultant headache, vomiting (often occurring in the early morning), and lethargy. On physical examination there may be papilledema, diplopia, hyperreflexia, ataxia, personality changes, and, if the process is far advanced, specific cranial nerve deficits or hydrocephalus. Supratentorial masses may present with seizure activity in addition to symptoms of ICP.

While the signs and symptoms of CNS neoplasms depend more on the site and size of the mass than on the histologic type, there are certain tumor types which predominate in childhood. In contrast to adults, children have a higher incidence (62%) of infratentorial tumors; these may occur in the cerebellum (medulloblastomas, ependymomas, and astrocytomas) or in the brain stem (astrocytomas and ependymomas). Supratentorial tumors, such as astrocytomas, ependymomas, and oligodendrogliomas, make up about 25% of cases.

Therapy of primary CNS neoplasms remains complex and controversial at this time. Neurosurgical removal of the tumor is agreed to be the initial treatment of choice for most lesions, but there often are instances where surgery is not feasible and other treatment modalities must be employed. Even in those cases of

complete (or near-complete) removal, malignant tumors have a high rate of recurrence if additional therapy is not given. In almost all cases it is necessary to give radiation therapy to the local site, the whole brain or to the entire neuroaxis. In conjunction with radiation, there is a rapidly developing role for chemotherapy in the adjuvant or even preradiation setting. Certain tumors such as medulloblastomas and high-grade astrocytomas have been studied most extensively and are the subject of ongoing large scale clinical trials (Allen 1985; Heideman 1989). It is as yet too early to make any recommendations concerning drugs or drug regimens for specific tumors, but there is optimism that chemotherapeutic agents may prove to have an important role in improving the survival rate of children with these tumors.

Neuroblastoma

Neuroblastoma is the second most common solid tumor of childhood, the first being brain tumor. It arises from neural crest tissue (adrenal medulla, sympathetic ganglia) with more than half of the cases presenting by 2 years of age. Approximately 60% of the tumors originate in the adrenal glands or retroperitoneum, although they may arise anywhere along the craniospinal axis. Most neuroblastomas secrete variable amounts of catecholamines (or their byproducts, i.e., VMA and HVA), which may be used to monitor the clinical course. There is no consistent hereditary pattern, but familial cases have been reported.

Unfortunately, neuroblastoma is widespread at diagnosis in approximately 70% of the cases. This fact, coupled with the tumor's notorious resistance to long-term control with current chemotherapy regimens, confers a poor prognosis for the majority of patients. Both age and stage of disease are prognostic factors. The Evan's staging system is used widely for treatment planning, although some use the Pediatric Oncology Group staging classification. Patients younger than age 1 year fare better than those above age 1, and those with Evan's stages I & II fare better than those with stages III & IV disease.

For patients with Evan's stage I (tumor confined to structure of origin) or II (tumor does not extend across midline) disease, treatment is limited to complete resection of the tumor. The overall survival rate for these patients exceeds 85%. For patients with stage III disease (tumor extends beyond the midline, or bilateral extension of midline tumor), treatment consists of surgery, postoperative radiation therapy, and chemotherapy. The overall survival rate for these patients is 20–70%. For patients with widespread disease at diagnosis (stage IV), the preferred treatment is autologous or allogeneic bone marrow transplantation after attainment of a complete remission by chemotherapy, surgical resection, and/or irradiation of localized residual disease. Under these circumstances, the overall survival rate is 30–40% (Graham-Pole et al. 1989). Without bone marrow transplantation, the survival rate is less than 5%. For patients with stage IV-S (stage I or II with involvement of the liver, skin, or bone marrow), no treatment or minimal treatment with chemotherapy will produce a 75% survival rate. Stage IV-S tumors often regress spontaneously with supportive therapy alone (McWilliams 1986).

A wide variety of chemotherapeutic agents has been used with a variable degree of success. Combinations of the following agents are currently being used: cyclophosphamide, VM-26, cisplatin, doxorubicin, vincristine, VP-16, DTIC, and melphalan. In addition, ^{131}I metaiodobezylguanidine (MIBG), a radioisotope linked to a monoclonal antibody, is being studied as a diagnostic as well as therapeutic tool.

Unfavorable prognostic factors include n-myc oncogene amplification (Brodeur et al. 1984), diploid tumor cell lines (Look et al. 1984), and high levels of serum ferritin, neuron-specific enolase, and serum LDH. Current research is focused on improving the chemotherapy and finding methods to improve the purging of marrow for autologous transplantation. In addition, progress has been made in early detection by screening infants for elevated levels of urinary catecholamines (Sawada et al. 1987).

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of childhood. It arises from embryonic mesenchyme that forms skeletal muscle. It is seen occasionally as part of a familial syndrome (Li-Fraumeni) of breast cancer, soft tissue and bone sarcomas, brain tumor, leukemia, and adrenocortical carcinoma occurring at unusually early ages (Li and Fraumeni 1982).

The entry of approximately three-quarters of the cases of RMS in the US on the Intergroup Rhabdomyosarcoma Study (IRS) has made it possible to study in detail the characteristics and treatment of this complex malignancy and improve survival rates (Maurer et al. 1988; 1989). Currently, the overall 3-year survival rate for patients treated on the IRS is greater than 70%, compared to less than 30% in the pre-IRS period (1963–1972). Information derived from this large IRS experience is extensive (Maurer et al. 1989).

RMS can arise almost anywhere in the body, but the most common sites are the head and neck, extremities, and genitourinary tract. Approximately 65% of patients are under 10 years of age at diagnosis, and the male to female ratio is 1.4. The tumor is widespread at diagnosis in 19% of cases. Embryonal histology is the most com-

mon type, followed by alveolar and botryoid. Embryonal and botryoid lesions tend to occur in young children and predominate in tumors of the GU tract and head and neck region. Alveolar lesions predominate in older children with trunk and extremity primaries. Genitourinary and extremity lesions tend to spread to regional lymphatics, whereas cranial parameningeal tumors invade the meninges early in the disease course. Prognostic factors include clinical group (stage), primary site, tumor size, histology and DNA ploidy of the tumor cell (Shapiro et al. 1989).

For a successful patient outcome, a coordinated multidisciplinary approach to patient management is required. Radical surgery (i.e., orbital exenteration, total pelvic exenteration, and radical head and neck surgery) rarely is needed to achieve local tumor control. However, local tumor control may be improved by primary re-excision after initial nondefinitive excision and by second-look surgery to evaluate response to nonoperative treatment and to resect any residual tumor. For patients with primary bladder tumors, survival after partial cystectomy (if feasible) is comparable to those undergoing early pelvic exenteration, and 90% have satisfactory bladder function. Surgery plays a central role in establishing disease stage and in the early identification of lymphatic spread (e.g.: in paratesticular and extremity lesions).

Radiotherapy is not required for optimal treatment of clinical group I (localized disease, completely resected, nodes negative) favorable histology (nonalveolar) disease. For some groups of patients (group II—regional disease grossly resected, nodes negative or positive) radiotherapy dose may be reduced to 4000-4500 cGy without compromising survival. However, for others (group III—gross residual disease; and group IV—metastatic disease) new approaches are needed to improve local control. An initiative in progress is the study of hyperfractionation radiation therapy schemes. CNS prophylaxis using radiation therapy and intrathecal chemotherapy for cranial parameningeal sarcoma dramatically increases survival from 45 to 65% at 5 years (Raney et al. 1987).

With currently available chemotherapy, maximum tolerated doses of combination therapy are required for cure, particularly for patients with localized gross residual disease after surgery. Intensive cyclic sequential actinomycin D plus vincristine provide durable control for 75% or more of patients with favorable histology groups I and II diseases. Repetitive pulse vincristine, actinomycin D and cyclophosphamide (VAC) is the combination of choice for group III disease, pending the outcome of IRS-III and -IV studies evaluating additional combinations. Doxorubicin and actinomycin D are equally effective components of this combination. No additional survival advantage has been gained by adding doxorubicin to the repetitive pulse VAC combination. Initiatives in progress in IRS-III include evaluation of cisplatin, VP-16, and intensification of chemotherapy for partial responders. Initiatives in pilot study for IRS-IV include evaluation of combinations which include ifosfamide, VP-16, and melphalan (Miser et al. 1987; Horowitz et al. 1988). Long-term control of metastatic disease remains elusive and will require novel approaches. Bone marrow transplantation has been disappointing thus far. Preparative regimens with better tumoricidal activity are needed.

Wilms' Tumor

Wilms' tumor, a malignant, embryonal neoplasm which arises in the kidney, is the most common intra-abdominal malignant tumor of childhood. The median age at diagnosis is approximately 3.5 years, and the male to female ratio is 1.2. Approximately 95% of the tumors are unilateral. This tumor may be seen in association with several congenital malformations, the most common being genitourinary anomalies, aniridia, hemihypertrophy, and Beckwith-Weidmann syndrome. Deletions of the short arm of chromosome 11 in the p13-14 band have been found in tumor cells.

The National Wilms' Tumor Study has contributed greatly to our understanding of this disease and its treatment (D'Angio et al. 1985). Tumors with unfavorable histology (anaplastic, clear cell, and rhabdoid types) are associated with a poor prognosis (Beckwith 1983). For all disease stages (I to IV), the overall survival rate is 80% or greater for patients with favorable histology tumors. The survival rate for patients with unfavorable histology tumors is 50–65%. Approximately 50% of patients with recurrent tumor can be saved. In contrast to patients with RMS and neuroblastoma, patients with hyperdiploid tumors do poorly.

Standard treatment is nephrectomy followed by chemotherapy for all patients, and postoperative radiation therapy for stages III and IV disease, all stages with clear cell or rhabdoid histologies, and stages II through IV with anaplastic histology. Chemotherapy consists of actinomycin D, vincristine, doxorubicin, and cyclophosphamide in two-, three-, or four-drug combinations. The length of treatment, the optimal drug dosing schedules and combinations, and the radiotherapy dosing are still the focus of ongoing studies. Cisplatin, VP-16, and ifosfamide are newer agents under study for patients with disease recurrence or at high risk of relapse.

Osteogenic sarcoma

Osteogenic sarcoma arises in bone-forming mesenchyme and is the most common primary malignant bone tumor in children. Long bones, especially

near the knee, often are the sites of occurrence. Spread of the tumor is hematogenous, usually to lungs, less so to other bones. It has its peak incidence at the time the child is most rapidly growing, i.e., at 14–15 years of age. Radiation-induced osteosarcoma is an entity that will be seen with increasing frequency because of the increasing population of long-term cancer survivors. These tumors arise in the field of previous radiation therapy at a median of 10 years after treatment.

Treatment strategy has changed dramatically in the past 15 years with the advent of effective chemotherapy (Link et al. 1986). In the absence of metastases, the standard approach in the past has been radical amputation followed by chemotherapy using a combination of agents including high-dose methotrexate with citrovorum factor rescue, doxorubicin, cisplatin, bleomycin, cyclophosphamide, and actinomycin D. This approach has resulted in a disease-free survival rate of approximately 60% compared to a disease-free survival rate of less than 10% with amputation alone. More recently, however, the approach has been to save the limb, if feasible, using preoperative chemotherapy followed by limb-sparing surgery, and then continuing the treatment with maintenance chemotherapy. The grade of tumor necrosis after preoperative chemotherapy, indicative of a histologic response to chemotherapy, is associated strongly with progression-free survival (Rosen et al. 1982). Current clinical trials are comparing preoperative chemotherapy followed by surgery versus initial radical surgery followed by chemotherapy. An additional question is whether the number of patients having a good histologic response can be increased using a different preoperative chemotherapy regimen. A newer active drug combination under clinical trial is ifosfamide and VP-16.

Unfavorable prognostic factors include metastatic disease at diagnosis, axial skeleton primary lesions, hyperdiploid tumor cell lines, large tumor size, and increased serum LDH levels (Look et al. 1988).

Ewing's Sarcoma

Ewing's sarcoma is the second most common malignant bone tumor of children and adolescents. The disease is diagnosed most commonly in the second decade of life and has a male predominance. Newer cytogenetic and immunohistochemical techniques are subdividing this rare tumor into categories, which in turn, may eventually have prognostic implications. Accumulating evidence suggests that the majority of these sarcomas are tumors of peripheral nervous system origin and have a chromosomal translocation (11;22) (q24;q12) identical to that seen in peripheral neuroepithelioma (Horowitz 1989). The primary location of the tumor is most often in the bones of the extremity, pelvis, and chest wall at diagnosis. Approximately 25% of patients have metastatic disease at diagnosis, primarily in the lung, bone, and bone marrow.

There is a controversy as to whether local tumor control is best achieved by radiation therapy or surgery. A reasonable approach is surgical resection of an expendable bone, such as the fibula or a small rib lesion. Furthermore, with preoperative chemotherapy and/or radiotherapy, limb salvage surgery is possible with modern orthopedic techniques. The local control rate with radiation therapy varies from 75 to 90%. All patients require chemotherapy for systemic disease control. The backbone of all chemotherapy regimens is the combination of vincristine, actinomycin D, cyclophosphamide, and doxorubicin, which produces a 70% disease-free survival rate at 2 years for patients with nonmetastatic disease and 20% for patients with metastatic disease. The combination of ifosfamide and VP-16 recently has been shown to have a high level of antitumor activity in patients with recurrent disease (Miser et al. 1987). This combination is being introduced into frontline therapy in current trials. Further areas of investigation include the use of cytokines that may allow an increase in chemotherapy dose intensity, the use of ICRF-187 which has the ability to prevent cardiac toxicity from doxorubicin, allowing increased use of this highly active drug, and autologous bone marrow transplantation for high-risk patients.

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