Pediatric Clinical Trials

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Key Words. Childhood tumors · Leukemia · Chemotherapy · Surgery · Radiation therapy

ABSTRACT

Clinical trials specifically tailored to the unique tumors and leukemias of children have resulted in increased survival rates approaching or exceeding 70% for most diseases. These studies have been carried out by investigators at large, independent institutions or through the auspices of the Children’s Cancer Group or Pediatric Oncology Group. The National Cancer Institute has also supported pediatric disease—focused efforts for rhabdomyosarcoma, Wilms tumor, Ewing’s sarcoma, osteosarcomas and other diseases. The present-day training of pediatric hematology/oncology fellows assures continuing contributions to the biology of childhood malignant lesions through applications of translational research. The Oncologist 1996;1:169-172

Annually about 7,500 American children younger than the age of 15 are diagnosed with cancer [1]. An almost equal number of adolescents between 15 and 21 years of age also will develop cancer. The Surveillance Epidemiology and End Results (SEER) Program of the National Cancer Institute has indicated that childhood cancer has increased from 12 cases per 100,000 in 1972 to nearly 14 cases per 100,000 in 1990 [2]. In spite of these statistics, cancer is relatively rare in childhood, but it remains the most frequent cause of death between late infancy and early adulthood and is exceeded only by accidents after the age of one year.

Clinical trials initiated since 1960 have had a profound effect on the overall survival of children with leukemia and solid tumors [3]. Whereas the survival rate of childhood acute lymphoblastic leukemia was about 5% in 1960, it now exceeds 70% [4-6]. In general, the five-year survival rates for patients with malignant solid tumors have increased from about 28% in 1960 to more than 70% by 1990 [7, 8]. Major strides have been made in the treatment of childhood Wilms tumor [9], Hodgkin’s [10] and non-Hodgkin’s lymphoma [11], and impressive gains have also been made in the survival rate of osteosarcoma [12], Ewing’s sarcoma [13] and rhabdomyosarcoma [14]. Major gains have also been accomplished for patients with neuroblastoma [15] and brain tumors [16].

By the late 1960s, protocols were established for the treatment of acute leukemias, Wilms tumor, neuroblastoma, Hodgkin’s disease, Ewing’s sarcoma and osteosarcoma, with the definition of treatment plans for each of these diseases. Staging schemes have been developed for quantitating the sites and extents of disease. Many of the staging schemes for pediatric cancers do not translate well to the tumor, node, metastasis schemes of the American Joint Committee on Cancer [17]. Evolving from these attempts at staging related to specific diagnoses have been changes in diagnostic imaging techniques which have allowed for development of such major steps as computed tomographic scanning, nuclear scintiscans and magnetic resonance imaging. The biological studies that have been possible for the various histologic subtypes of the lymphoma, leukemia, rhabdomyosarcoma, Ewing’s sarcoma, neuroblastoma and Wilms tumor have established certain clinical and biological risk factors which may be innately related to prognosis outcome. Along with designated staging criteria, uniform response criteria have been developed for childhood leukemias and for solid tumors. Biostatistical analysis of results of the past has led to the involvement of biostatisticians in planning clinical protocols to obtain ongoing analysis of results, early stopping rules and definition of the numbers of individuals admitted so as to answer the specific questions of the trial.

Pediatric clinical trials have led to the treatment of leukemic patients with chemotherapy with or without irradiation, and solid tumors with multiple modalities including surgery, chemotherapy and irradiation. The possible surgical
techniques for various anatomical regions of the body are too numerous for discussion; however, when the tumor is large and potentially unresectable, or resectable only with significant morbidity, presurgical chemotherapy and/or radiation-chemotherapy have become standard for such diseases as Wilms tumor, neuroblastoma, Ewing’s sarcoma and soft-tissue sarcomas. Definition of the order of the modalities, or which modalities may be combined, is related to the histologic type of tumor and extent of disease. For example, for a large Wilms tumor crossing the midline, surgery can be greatly facilitated through the use of presurgical chemotherapy. Similarly, after biopsy of a bone lesion suspected of being osteosarcoma, chemotherapy may potentially provide a significant reduction in tumor size, facilitating successful resection of the tumor and the placement of an endoprosthesis. For neuroblastomas in which there is found to be bone marrow disease at diagnosis, a “second-look surgery” may become definitive surgery for removal of an adrenal or retroperitoneal primary tumor with nodal metastases.

The National Cancer Institute organized several groups for the treatment of childhood cancer in the late 1950’s. These organizations, including the Children’s Cancer Study Group (the predecessor of the Children’s Cancer Group [CCG]), Cancer and Leukemia Group B (CALGB) and the Southwest Cancer Chemotherapy Study Group (SWCCSG), developed numerous protocols in the early 1960s and 1970s primarily related to the treatment of childhood acute lymphoblastic leukemia. In 1980, the Pediatric Oncology Group (POG) was formed by pediatric institutions which were formerly members of the Southwest Oncology Group (successor to the SWCCSG) and CALGB. The efforts of the POG and the CCG have resulted in organized treatment schemes and protocols for most of the major types of childhood cancer. Through the high standards of these groups, many clinical and biological contributions have been made, some of which have been the models for subsequent development of treatment programs for cancers occurring primarily in adults. At the present time, most of the pediatric clinical trials in the United States and Canada are conducted by these two cooperative pediatric groups.

The National Cancer Institute independently funds studies for the treatment of Wilms tumor (National Wilms Tumor Study) [9], and rhabdomyosarcoma (Intergroup Rhabdomyosarcoma Study) [14]. Studies may be conducted jointly by the CCG and POG groups for other diseases such as Ewing’s sarcoma [13], osteosarcoma and germ-cell tumors. The accruals to these major cooperative groups include more than 5,000 patients annually.

Other large pediatric cancer centers such as Memorial Sloan-Kettering Cancer Center, MD Anderson Hospital, Dana-Farber Cancer Center, Children’s Hospital at Stanford, The Mayo Clinic and St. Jude Children’s Research Hospital have ongoing outreach programs with affiliated institutions in geographically near or distant areas. These institutions also have ongoing “in-house” clinical trials for many of the more common pediatric neoplasms.

In addition to cancer trials of pediatric subjects in this country and Canada, there are organized ongoing national cooperative trials in the United Kingdom, France, Germany, Italy, Switzerland, Japan, Argentina, Brazil and Australia-New Zealand. The International Society of Pediatric Oncology (SIOP), with active members in Europe, the Middle East, Africa, the Far East and North and South America, actively promotes clinical trials for numerous categories of diseases. At its annual meetings, updates of ongoing trials are presented and new protocols approved. The annual meetings serve significantly as a time for exchange of information among pediatric oncologists, pediatric radiation oncologists, pediatric oncologic surgeons, epidemiologists and parents of childhood cancer patients.

There are several reasons for support of drug development for pediatric cancer. The agents active in childhood cancer may differ from the agents given the highest priority for development of cancers in adults [18-23]. The screening of new agents by the National Cancer Institute includes a panel of 60 tumor cell lines; pediatric tumor cell lines are not represented within the panel [24]. Specifically, there are few cell lines in the screening panel of the National Cancer Institute that have been developed for pediatric rhabdomyosarcoma, osteosarcoma, neuroblastoma, Ewing’s sarcoma, gliomas or other predominant childhood neoplasms. Other reasons for support of these drug trials in pediatric patients are that the toxicities of phase I and biologic-response-modifying agents may be unique to children. The pharmacokinetics also may differ for children in that pediatric subjects often tolerate higher doses of chemotherapeutic agents.

Standard pediatric clinical trials have contributed to the integration of new chemotherapeutic agents into the standard therapy of many tumors. For example, the use of high-dose methotrexate has been incorporated into trials for osteosarcoma following the trials of escalated doses of methotrexate at the Dana-Farber Cancer Center [25]. Similar trials conducted in the early 1970s included the evaluation of doxorubicin (which has been found to be an important contributor to the treatment of osteosarcoma), Ewing’s sarcoma, soft-tissue sarcomas and neuroblastoma [26-28]. Cisplatin became available in the late 1970s [29], while the epipodophyllotoxins [30], carboplatin [31] and ifosfamide became available in the 1980s [32-34].

Phase I trials have identified agents which are presently being looked at in patients at high risk for treatment failure for such primary diseases as rhabdomyosarcoma, osteosarcoma and Ewing’s sarcoma. The utilization of the “window of opportunity” approach to the delivery of agents identified
in phase I and II trials may be useful in the treatment of patients with high-risk features [35]. Such “up-front” trials have identified agents worthy of inclusion in multi-agent trials for standard-risk patients.

The Food and Drug Administration has begun to include a “pediatric use” section in the labeling of drugs [36]. This information will indicate the basis for the information and will indicate “if the course of the disease and the effects of the drug, beneficial and adverse, are sufficiently similar in the pediatric and adult populations, then the adult experience can be used in the pediatric population.” Additionally, “Pediatric use information under the new regulation may consist of data on the pharmacokinetics of the drug in the pediatric population or other data to permit determination of appropriate dosage. It may also include data from pharmacodynamic studies of the drug in the pediatric population, data from other pediatric clinical trials, data on adverse events. If there is no substantial evidence to support any pediatric use, or use in a particular pediatric population, this must be stated [36].”

Since few of the individuals treated by pediatric oncologists have obtained all or most of their expected development, quality-of-life issues become important even before definitive diagnosis is established [37]. In concert with pediatric surgeons, radiation oncologists, nurses, nurse practitioners, physicians’ assistants, social workers and rehabilitation specialists, the pediatric oncologist directs the plans for long-term care which may be initiated prior to making a diagnosis. With the cure of so many childhood cancer patients, planning for future events of acute or chronic nature is considered in the planning of pediatric clinical trials. Subtle or not-so-subtle complications or late effects are considered to be of equal or greater importance than acute effects. While cure is the primary objective, the growth and development of the central nervous system, pulmonary, cardiac, renal, hepatic and intestinal functions or other organ systems are considered in the planning of multimodality treatment because of the possible late complications influencing one or multiple organ systems. Planning also considers the late development of secondary neoplasms which may be genetically influenced or associated with prior radiation or chemotherapy [38-40]. Lifelong follow-up in specialty clinics for survivors of childhood cancer is essential for these individuals to become worthy contributors to society. Assurances must be made for the educational opportunities, insurability and societal contributions of the survivors of childhood cancer, as it is estimated that by the year 2000, 1 in 900 individuals will be such a survivor.

Pediatric oncologists are also involved in steps related to prevention of cancer. Survivors of childhood cancer should receive counseling regarding health-promoting lifestyles. Screening of individuals at high risk of developing cancer may include individuals with abnormalities of the p53 [41, 42] or p16 genes [43, 44]. Efforts also have been directed toward familial studies of individuals with retinoblastoma, Wilms tumor with hemihyper trophy and adenomatous polyposis coli. Investigators have been involved in screening for the early detection of neuroblastoma in Japan [45] and elsewhere.

At this time, and in the future, we can expect pediatric oncologists to play a significant role in translational research—the utilization of laboratory-based results and their application to clinical pediatric oncology practice. The American Board of Pediatrics Sub-Board in Hematology/Oncology presently requires that fellows in training demonstrate a meaningful accomplishment in research in addition to clinical competence in that subspecialty of at least one year’s duration. It is from these present and future pediatric hematology/oncology fellows that future biological and clinical accomplishments and improvements will be assured.

**Acknowledgments**

This work was supported in part by Childhood Cancer Center (CORE) Grant CA-21765 and Solid Tumor Project Grant CA-23099 from the National Cancer Institute, and by the American Lebanese Syrian Associated Charities (ALSAC).

**References**