Evolution of Modern Treatment of Childhood Acute Leukemia and Cancer

Adventures and Battles in the 1970s and 1980s

Yaddanapudi Ravindranath, MBBS

KEYWORDS

• Treatment of Acute lymphoblastic leukemia • Central nervous system leukemia
• History of Childhood acute leukemia and cancer • Aminopterin • Subbarow

KEY POINTS

- The success in childhood leukemia illustrates how treatment programs were designed using clinical- and biology-based risk factors seen in the patients.
- In the mid-1960s a principal focus in curing childhood leukemia entailed control of the central nervous system part of the disease.
- New frontiers were explored and new supportive disciplines were established that paved the way for the current molecular era, which promises to discover new targets for therapy so that we can achieve high cure rates with low morbidity in children with cancer.

The search for understanding is an adventure or more commonly is a series of adventures…Now that geographical boundaries in our own and in other civilized lands have been determined, the pioneering spirits found in scientific research find enticing vistas for adventure.

—Walter B. Cannon

The Way of an Investigator
—Quotation from the foreword to Pediatric Clinics of North America, v.9, no. 3, 1962, issue on Hematology by Editor Carl H. Smith.

When I received the invitation from *Pediatric Clinics of North America* to guest edit an issue on pediatric oncology, I gladly accepted this challenge, as it gave me an opportunity to present the advances from a perspective of one who started a career in pediatric hematology oncology when the cure rates were abysmally low in contrast to the

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Department of Pediatrics, Wayne State University School of Medicine, 3901 Beaubien Boulevard, Detroit, MI 48201, USA
E-mail address: ravi@med.wayne.edu

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optimism for curing all children with cancer now—current estimates project nearly 80% long-term survival rate for all children with leukemia and cancer. A quote from Dr Sanford Leiken's section in the 1962 issue of *Pediatric Clinics of North America* on Leukemia: Current Concepts In Therapy illustrates status of childhood cancer therapy in the early to mid-1960s, "At present acute leukemia of childhood is not curable, but it is treatable; although fatal, it can be controlled in varying periods of time so that the patient's life can be prolonged in a relatively comfortable and functional state."[1] It was in this milieu that I started my own career. The task of caring for children was grim indeed. Our standard opening dialogue with parents of a child with leukemia (most cancers) newly diagnosed started with the sentence "Your child has leukemia/cancer and there is no cure for it."

One of my first experiences was coming across several children with leukemia who were long survivors, many of whom were included in the original publication of long survivors written by Joseph Burchenal and M. Lois Murphy from Sloan-Kettering Institute of Cancer Research and Cornell University Medical College in New York.[2] In this publication, Drs Burchenal and Murphy attempted to list all of the known survivors of acute leukemia from direct correspondence with hematologists in the United States. There were 71 patients with acute leukemia living 5 years or more from diagnosis at that time. Of those, only 36 were living with no evidence of leukemia. A large cohort of these patients had come from Children's Hospital of Michigan and was treated under the direction of Wolf W. Zuelzer, my mentor, and mentor to noted pediatric oncologists - Sanford Lieken, William Newton, and Theresa Vietti.[3,4] One of the patients (GB) in the Burchenal cohort was a child with acute lymphoblastic leukemia (ALL) treated in 1952 who I tried to contact in preparation for a report on long survivors in childhood leukemia. To my disappointment, the parents did not permit me to contact the young man, as at that time the practice was to not tell the children of their diagnosis. He received aminopterin for a total of 10 months, the first generation of antifolates synthesized by Yellapragada Subbarow of Lederle Laboratories.[5] This is one of the antifolates first used by Sidney Farber; although, in his famous article, Dr Farber failed to include Dr Subbarow as coauthor, an astonishing omission considering that Subbarow synthesized the antifolates specifically for treatment of childhood leukemia at Dr Farber's request.[6] As things turned out, I discovered patient GB at a fundraising golf outing in 1998 and fortuitously earlier this year, through a colleague at another golf event, he reestablished contact with me.[7] Now 67, one of the longest survivors of childhood leukemia, he is doing well and has a thriving engineering business.

In the next few paragraphs I summarize the adventures and explorations in the 1970s and 1980s in the treatment of children with leukemia and cancer that paved the way for the current success in childhood cancers. Indeed, these were adventures and bold steps into unchartered waters. Because childhood leukemia is the most commonly known childhood cancer, success in childhood leukemia was pivotal in the push toward cure of all childhood cancers. The success in childhood leukemia illustrates how treatment programs were designed using clinical- and biology-based risk factors seen in the patients. Thus, in the mid-1960s, although the remission/induction rate was quite respectable by even current standards, relapse occurred frequently, and the overall cure rate still remained less than 10%. A major problem in child ALL was relapse at extramedullary sites, most often in the central nervous system (CNS). A collage of the types of extramedullary disease we were seeing is shown in **Fig. 1**. Hence, a principal focus in curing childhood leukemia entailed control of the CNS part of the disease. Concurrently with these attempts, new developments were occurring rapidly in the immunophenotyping and karyotyping of the childhood leukemias and thus a better definition of the molecular biology and risk factors for the type