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Milestones in the Curability of Pediatric Cancers

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Progress in the study and treatment of childhood cancer is arguably the most remarkable and rewarding story of cancer therapy in the past five decades. During this time, five-year survival rates have steadily increased and now exceed 80% in developed countries for all pediatric cancer sites (Fig 1).[1] With the expectation of extended survival into adulthood for most childhood patients with cancer, clinicians and researchers have concentrated considerable attention on optimizing the quality of long-term survival for diseases that largely respond to cytotoxic agents and modalities injurious to normal tissues. In this recollection of that progress, we shall touch on advances common to many childhood cancers but focus primarily on childhood leukemia because it has been the bellwether of scientific and therapeutic advances in many tumors, it encompasses many novel ideas in patient care during and after therapy, and it has influenced the study and treatment of adult cancers as well.

Evolution of the Pediatric Acute Lymphoblastic Leukemia Treatment

Table 1 summarizes factors motivating treatment evolution and progress in childhood acute lymphoblastic leukemia (ALL). Before 1950, childhood acute leukemia was not differentiated into ALL or acute myeloid leukemia. A diagnosis of childhood leukemia was uniformly fatal within an average period of 3 months. Death resulting from hemorrhage and severe infection was routine, and blood transfusions, the only treatment available at the time, were occasionally tried but did not help. Approximately 80% of these patient cases were later identified as having childhood ALL; that is still approximately the percentage of cases found today.

From 1950 to 1960, dramatic changes in treatment occurred. Farber et al[2] were the first to try chemotherapy in children with leukemia. Farber initially tested folic acid, because it was used to treat pernicious anemia and the bone marrow morphology of the two diseases looked similar. However, when folic acid seemed to make the leukemia worse, Farber decided to take the reverse approach and try aminopterin, an analog of methotrexate that interferes with folate metabolism. Also in this decade, George Hitchings and Gertrude Elion, who subsequently won the Nobel Prize, created 6-mercaptopurine specifically to interfere with DNA metabolism.[3] And cortisone, which was considered the new miracle drug, and prednisone were prescribed for many refractory diseases at the time, including leukemia. All these drugs were given as single agents that sometimes produced a transient response; ultimately, all patients died.

From 1958 to 1962, the first systematic combination chemotherapy trials for the treatment of leukemia were conducted primarily in children by Emil Frei and Jay Freireich of the National Cancer Institute, Donald Pinkel and James Holland from the Roswell Park Cancer Institute, Joseph Burchenal from the Memorial Sloan-Kettering Cancer Center, and others. The therapy was based primarily on two research findings: first, tuberculosis in humans that became resistant to single antibiotic therapy responded to triple-drug combinations; second, promising therapeutic studies using L1210 leukemia murine cell lines were tried in humans.[4,5] These combinations resulted in remissions defined by transient improvement in symptoms (eg, stamina, appetite) and resolution of signs of bone marrow failure (eg, petechiae); but again, all patients eventually succumbed to the disease.
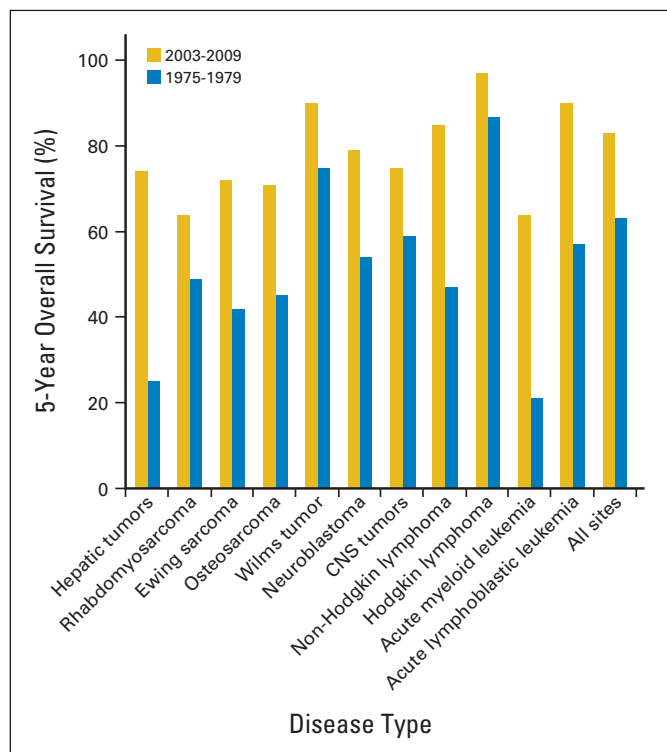

Fig 1. Five-year survival rates for two time periods for pediatric cancer diagnosed from birth to 19 years old. Five-year survival is presented for all sites (International Classification of Childhood Cancers) and specific histologic subtypes contrasting outcomes for children diagnosed between 1975 and 1979 with those diagnosed between 2003 and 2009. Data obtained from the National Cancer Institute SEER program from nine SEER registries based on patient cases observed through 2010.[1]

Decade	Treatment Progress During Decade	Factors Motivating Change
	Table 1. Factors Motivating Treatment Evolution and Progress in Childhood Acute Lymphoblastic Leukemia	
1960s	Use of single-agent chemotherapy (methotrexate, mercaptopurine, vincristine, asparaginase, cyclophosphamide, daunorubicin, and cytarabine) Introduction of combination chemotherapy treatment protocols Standardization of therapy phases (remission induction, consolidation, CNS therapy, maintenance)	Demonstration of antileukemic activity among agents interfering with cellular metabolism Recognition that single-agent therapy produced transient responses Emulation of combination therapy approach successful in resistant tuberculosis and preclinical mouse models Appreciation of need for CNS-directed therapy with early use of cranial and craniospinal irradiation
1970s	Integration of anthracyclines in therapy protocols for high-risk ALL Demonstration of improved outcomes with use of therapy intensification and delayed intensification Reduction in use of spinal irradiation for CNS	Recognition of diverse ALL pathobiology and outcomes Appreciation of clinical factors that influence treatment outcomes (age at diagnosis, initial leukocyte count, response to treatment) Identification of pathobiologic differences in ALL that influence outcome (immunophenotype, cytogenetics, chromosomal translocations, chromosomal ploidy) Demonstration of comparable outcomes using craniospinal irradiation and cranial irradiation plus intrathecal chemotherapy
1980s	Integration of asparaginase intensification in therapy protocols for high-risk ALL Restriction of epipodophyllotoxin use for most children with ALL Reduction in use of cranial irradiation therapy for CNS-negative ALL	Appreciation of delayed neurocognitive and neuroendocrine toxicities after cranial irradiation Recognition of treatment-related acute myeloid leukemia associated with epipodophyllotoxins Demonstration that intensified (triple) intrathecal chemotherapy could sustain CNS remissions without the use of cranial irradiation in patients with standard-risk ALL
1990s	Introduction of imatinib for Philadelphia chromosome–positive ALL Integration of dexamethasone in induction therapy protocols Reduction in dose and use of preventive cranial irradiation Recognition of role of host pharmacogenomics in chemotherapy-related toxicity and ALL response Implementation of risk-stratified treatment protocols on the basis of ALL pathobiology	Identification of novel antileukemia drug targets on the basis of molecular and cellular changes stimulating leukemia development (eg, *BCR-ABL*) Recognition of radiation-related subsequent neoplasms Recognition of dose-related risk of anthracycline cardiotoxicity Recognition of dose-related risk of cyclophosphamide gonadal toxicity Demonstration of superiority of dexamethasone compared with prednisone in preventing CNS relapse
2000s	Personalization of therapy related to early treatment response (minimal residual disease) Elimination of use of cranial irradiation for most children with ALL Investigation (ongoing) of molecular targets for drug development	Demonstration of prognostic significance of minimal residual disease Recognition of role of pharmacogenomics in treatment response and acute/delayed toxicities Identification of novel leukemia subtypes on the basis of alterations in cellular signaling

Abbreviation: ALL, acute lymphoblastic leukemia.

From 1960 to 1967, physicians formulated diagnostic criteria for childhood leukemia. They designated continuous complete remission as the gold standard of success, and established the disease subtypes by ordinary light microscopy. At the time, there were several obstacles to effective therapy: the disease was widespread at diagnosis; localized therapy was basically ineffective; and both the disease and the therapy damaged the bone marrow, which frightened the medical community. And of course, physicians were ignorant of the pathogenesis of the disease and why drugs succeeded or failed, which remains a problem today.

There were additional obstacles to cure. First of all, there was a fear of chemotherapy, and some eminent hematologists were the most antagonistic toward chemotherapy. Many hematologists in large medical centers were strongly opposed to giving chemotherapy (often referred to as poisoning children), and a misguided protectionism to shield children from further suffering was the prevailing attitude. There was also a distrust of clinical trials and protocols, which were dubbed cookbook medicine by some physicians who did not want to be told how to treat their patients. Pessimism and provincialism, especially in medical schools, were also obstacles to cure. St Jude Children's Research Hospital and other institutes were looked down on because they were not in the academic mainstream, which in the long run turned out to be an asset rather than a liability.

Despite these obstacles, amazing progress was made from 1960 to 1967. Vincristine, asparaginase, cyclophosphamide, daunorubicin,

and cytarabine were all introduced into clinical use in that narrow window of time. The importance of the phases of therapy—remission induction, intensification, consolidation, CNS therapy, maintenance, and so forth—was beginning to be recognized. CNS involvement became a major problem with achievement of prolonged bone marrow remissions. On the basis of mouse studies, Pinkel et al elucidated the concept of occult meningeal leukemia and the importance of presymptomatic CNS-directed therapy.[6-8] Without specific CNS therapy, CNS relapse preceded bone marrow relapse in an increasingly higher proportion of patients.

Considering these observations, the early St Jude Total Therapy studies culminated in the pivotal Study V that changed the direction of the treatment of childhood leukemia.[6,9] The study design called for the maximum tolerated dose of chemotherapy, aggressive supportive care, and better CNS prophylaxis. Prednisone and vincristine were administered as induction therapy followed by an intensive phase of high-dose 6-mercaptopurine, methotrexate, and cyclophosphamide given intravenously during a 7-day period. A lymphomacidal dose of 2,400 cGy cranial radiation plus intrathecal methotrexate was administered during 2 1/2 weeks. Patients received 6-mercaptopurine once per day, methotrexate and cyclophosphamide once per week, and prednisone and vincristine twice every 10 weeks. With this approach, which is similar to the treatment model used today, 31 of 35 consecutive patients attained complete remission and received all phases of

therapy. Not a single patient relapsed in the first 6 months, and 50% of patients were long-term survivors in continuous complete remission.[10] Subsequent trials during the 1970s established the benefit of delayed intensification therapy after remission induction and further advanced long-term survival rates to almost 70%.[11-14]

Developing the Risk-Directed Therapy Paradigm

With the establishment of an effective portfolio of agents, clinical trials in the last three decades have focused on risk stratification and application of intensified regimens to targeted subsets of patients to advance survival rates and reduce treatment-related morbidity and mortality. Strategies for risk categorization during this time have been based on age at diagnosis, initial leukocyte count, leukemic cell genetics, and initial response to treatment.[15] Progress in the understanding of ALL pathobiology permitted more informed risk assessment using immunophenotyping, cytogenetics, immunophenotype-specific chromosomal translocations, and modal chromosomal number (ploidy). Survival outcomes for childhood ALL in the last four decades derived from the SEER program data from 1975 to 2009 illustrate the collective success of these efforts nationwide (Fig 1), with results from specific groups demonstrating even better outcomes.[16-18]

In recent years, initial response to treatment as determined by minimal residual disease has provided an assessment of drug sensitivity as well as host pharmacodynamics and pharmacogenomics and treatment adherence; this technology has permitted more precise risk stratification.[15] Characterization of the molecular and cellular changes stimulating cancer development elucidated novel targets for anticancer drug development. The first among these was the identification of the Philadelphia chromosome in ALL,[19] which ultimately led to the successful use of targeted therapy with imatinib, a selective inhibitor of the BCR-ABL1 tyrosine kinase.[20] Genetic expression profiling, mutational analyses, and genome-wide analyses have enabled recent discoveries of novel leukemia subtypes with alterations in cell signaling that may benefit from targeted therapy.[21-24]

Late Health Outcomes As a Driver of Therapy Evolution

Observational studies of late health outcomes among long-term survivors of ALL have been a major impetus for therapy change. Initially, concerns regarding delayed neurocognitive[25-27] and neuroendocrine dysfunction[28-33] associated with cranial irradiation motivated several cooperative group trials that established that intensification of intrathecal chemotherapy with either methotrexate alone or methotrexate in combination with hydrocortisone and cytarabine could sustain CNS remissions without the use of cranial radiation.[34-36] These data, combined with evidence of the superiority of dexamethasone compared with prednisone[37] in preventing CNS relapse were influential in the design of recent trials that have eliminated cranial irradiation.[18] Recognition of treatment-related subsequent neoplasm, such as radiation-related CNS malignancies[38-41] and epipodophyllotoxin-associated secondary leukemia,[42-46] has also been a powerful stimulus for restricting the use of these modalities in contemporary regimens.

Appreciation of a pediatric-specific threshold for anthracycline cardiotoxicity among children with ALL[47-51] prompted evaluation of the cardioprotectant dexrazoxane and continuous infusion anthracycline administration in first-line trials.[52-54] Whereas adult studies demonstrated an excess risk of anthracycline-induced congestive

heart failure after treatment with cumulative doses of 550 mg/m^2 or higher,[55] children are more vulnerable to this complication at lower cumulative doses and debate continues regarding whether any dose is truly safe.[56-58] Lacking echocardiographic evidence of long-term benefit of preventive measures, anthracycline doses are proactively restricted in contemporary regimens with higher cumulative doses reserved for children and adolescents with unfavorable risk disease features. Similarly, a risk-adapted approach guides the dosing of cyclophosphamide in an effort to optimize leukemic response and preserve fertility of long-term survivors, especially for boys, who are more susceptible to alkylating agent germ-cell injury than girls.[59]

The achievement of extended survival into adulthood for most children with ALL produced compelling evidence of the scope and severity of treatment-related adverse effects and their contribution to premature mortality and reduced quality of survival.[60-65] These observations motivated investigations aiming to more accurately characterize risk profiles for adverse outcomes to facilitate risk-adapted treatment assignment (when possible) and timely diagnosis and intervention to prevent or remediate morbidity.[66] Numerous studies have elucidated factors influencing the risk for neurocognitive,[67-71] skeletal,[71-83] cardiovascular and metabolic,[31,50,56,57,84-86] and neoplastic complications[38,39,41-43,45,46,87] related to the individual patient as well as sociodemographic status and cancer history. An active area of investigation in more recent years is the study of how genetic variations influence not only response to antileukemia therapy[88,89] but also the risk of long-term and late cancer treatment–related toxicity.[56,69,81] This research has focused largely on single nucleotide polymorphisms that affect drug disposition and normal tissue recovery from cytotoxic therapy. Findings from this line of study may ultimately permit more precise risk characterization that can be used to guide treatment planning and toxicity monitoring.

Translating Findings of Outcomes Studies Into Survivorship Care

Despite substantial research linking specific cancer therapies with adverse outcomes, limited high-quality research exists evaluating the risks, benefits, and harms of health screening and health promoting interventions among high-risk groups. Given the relatively small numbers of pediatric cancer survivors, their variable access to pediatric late effects research programs, and the delayed time to presentation of many outcomes, implementation of randomized controlled trials in asymptomatic survivors to assess the impact of screening on morbidity and mortality associated with a specific late effect is challenging and often not feasible. Notwithstanding these deficiencies, clinical practice guidelines for the management of asymptomatic long-term survivors of childhood, adolescent, and young adult cancers have been organized by several groups to standardize the care of this medically vulnerable and growing population. Recommendations have been developed from a hybrid approach that uses evidence from the extant literature linking late effects with therapeutic exposures and formulates screening recommendations on the basis of the clinical experience of late effects experts, matching the magnitude of the risk with the intensity of screening.[90,91] The currently available clinical practice guidelines have been useful in identifying research priorities to address knowledge gaps in survivorship care such as who may benefit from screening, the time to initiate screening, the frequency of screening, and the optimal modality of screening.[92,93]

Standardizing survivor care also enhances opportunities for discovery of novel and unanticipated treatment effects and provides critical information to guide the development of health-promoting interventions. Consistency of cardiac screening among a well-characterized cohort of children with ALL advanced understanding of the pathophysiology of anthracycline cardiotoxicity[48-50] and informed clinical trials to prevent and remediate this complication.[53,54,94,95] Proactive screening of neurocognitive functioning has also been instrumental in discerning outcomes of evolving CNS-directed therapy among children and adolescents[68,69,96-98] and guiding interventions[99,100] to optimize their educational and vocational achievement. With increasing numbers of adults treated for ALL during childhood, the challenge will be to understand how cancer treatment impacts natural organ senescence and translate this knowledge into interventions to promote healthy aging.

Challenges to Achieving Future Progress

The treatment paradigm that produced long-term disease-free survival in childhood ALL has been embraced as the standard for all pediatric cancers and continues to be highly supported by physicians, patients, and their families. Major factors in the success of therapy for pediatric cancer care are a multidisciplinary team approach and a preference for delivery of therapy in the context of a clinical trial. A fundamental tenet of these trials is the integration of biologic and therapeutic aims facilitated through the collection of tumor tissue. This factor has contributed substantially to advancing understanding about the heterogeneity of pediatric cancers across and within histologic subtypes and guided the development of risk-stratified therapy for a variety of hematologic and solid pediatric malignancies.[15,101-104] For example, treatment planning for children with acute myeloid leukemia,[104] non-Hodgkin lymphoma,[105] Wilms tumor,[106] neuroblastoma,[101,102] and rhabdomyosarcoma[107,108] routinely considers biologic factors (eg, histology, grade of tumor differentiation, DNA ploidy, chromosomal alterations, MYCN oncogene status). In neuroblastoma, international collaboration has permitted characterization of highly prognostic pretreatment clinical and biologic features that will facilitate the comparison of future risk-based clinical trials.[102] In addition, clinicopathologic and biologic studies have identified prominent pathways (eg, FLT3, tropomyosin-related kinase B, vascular endothelial growth factor)[109-111] and surface markers (eg, anti-GD2)[112] in malignant cells that have enabled the development of targeted therapies that are in use or under investigation.

Ongoing biologic research aims to identify novel therapeutic targets by clarifying the molecular drivers of disease at diagnosis and how these may change at relapse. Following the paradigm that benefitted patients with ALL with Philadelphia chromosome–positive ALL with the use of tyrosine kinase inhibitor of BCR-ABL1, a variety of molecular targets for pediatric malignancies are under investigation.[113-115] This burgeoning area of research may ultimately guide the development of effective therapies with a lower risk of normal tissue injury. However, the undertaking of such studies in pediatric patients with cancer faces challenges on several fronts. First, the relative rarity of pediatric cancer reduces the priority assigned for new agent research and development by the pharmaceutical industry and the National Cancer Institute.[116] Likewise, the biologic diversity between and within histologic subtypes limits the feasibility of recruitment of sufficient patient numbers to ascertain statistically powerful outcomes. Cooperative group and international collaboration will

undoubtedly be needed for many diseases to establish treatment efficacy for new agents and accumulate the evidence required for their regulatory approval. Integrating targeted agents into first-line therapies will also require innovative clinical trial designs that consider the disease-free outcomes achieved with established cytotoxic treatment approaches as well as the potential for reduction in adverse events known to compromise quality and duration of survival. Clinicians will also have to contend with the ethical dilemma of testing novel regimens substituting targeted, presumably less toxic, agents for cytotoxic agents included in highly successful treatment approaches.

Appreciation of the unintended consequences of historic treatment approaches has engendered the commitment by pediatric investigators to continue systematic documentation of adverse health outcomes among childhood cancer survivors treated with contemporary therapy. Consequently, clinical trial funding must extend beyond the therapeutic objectives to include evaluation of late effects. Research characterizing genetic predispositions associated with increased vulnerability to acute and late treatment-related toxicity may guide the delivery of safer personalized therapy in the future. In this regard, researchers of pediatric ALL have completed pioneering investigations that have established correlations between genetic variations influencing antileukemic drug metabolism and distribution that contribute to treatment response, acute toxicity, and risk of late effects.[69,72,81,89,117-119] Similar investigations involving diverse pediatric malignancies are exploring the genetic risk factors underlying other adverse outcomes such as cardiomyopathy and obesity.[56,86,120,121] These efforts will be critical to defining the optimal therapeutic approach that balances the attainment of cancer-free survival with prevention of long-term and late treatment toxicities, particularly life-threatening toxicities.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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