Introduction

A Brief History of Childhood Cancer Treatment

Childhood cancer is often pointed to as a modern success story of medical research, a story that began more than 50 years ago with the initial treatment of children with acute lymphoblastic leukemia (ALL). In the 1960s, a child with ALL—the most common childhood cancer—had a less than 10% chance of being cured. A child diagnosed with ALL today has almost a 90% chance of being cured. In that relatively brief period of history, similar advances were made in several childhood cancers, including Wilms tumor and pediatric lymphomas (Fig. 1A). However, progress with other childhood cancers has varied and, in certain cases, been significantly more limited. Today, almost 40% of the children diagnosed with acute myelogenous leukemia (AML), 66% of children diagnosed with high-risk neuroblastoma, and greater than 95% of children with brainstem glioma die from their disease (Fig. 1B). In fact, despite remarkable progress made, childhood cancer remains the leading pediatric cause of death from disease in the United States.

Understanding the basis for success in treating children with ALL can help inform the challenges faced today in finding more effective treatments for children with cancer. The 5-year survival for children with ALL improved at a steady pace from the 1970s through the 1990s (Fig. 2). One could surmise that this period was a time of major new drug discoveries. Quite remarkably, almost all of the drugs used in the treatment of childhood ALL that drove this improvement were primarily discovered and developed in the 1950s and 1960s (for US Food and Drug Administration [FDA] approval years, see Table 1). If it was not new drug discovery that drove improvements in outcome, then what were the driving forces? Several factors contributed to this transformation in outcome. Central to improvements were the increasing discoveries focused on understanding the heterogeneity of childhood ALL; it is not a single disease but rather an evolving group of diseases with differing biologic characteristics. Initially, phenotypic and demographic markers (white blood cell count, patient age) identified subgroups of patients requiring more intensive treatment; this was followed by methods to quantify initial response to therapy and progressed to defining subgroups of patients by molecular markers. The advances during the 1960s in use of platelet transfusion for the treatment of thrombocytopenia led to the ability to better support children through periods of...
myelosuppression from a spectrum of effective but myelo-
suppressive drugs. Starting in the 1970s and extending into
the 1980s, the fundamental principles surrounding support-
ive care of the immunocompromised host were defined.
These principles included the institution of preventive
treatment for opportunistic infections (eg, Pneumocystis jir-
oveci, formerly Pneumocystis carinii) as well as standardized,

systematic approaches to the evaluation and treatment of children with febrile neutropenia. This was followed by
the development of cytokines (eg, granulocyte colony-
stimulating factor), which allowed for an even further
intensification of treatment in subgroups of children.
And throughout this entire period, the ability to care for
critically ill children improved. The sum total of these
efforts allowed for increasingly intensive chemotherapeutic
approaches in children with higher risk subtypes of ALL
using drugs that were first discovered and developed in the
1950s and 1960s.

Perhaps not surprisingly, improvements in outcome
through intensification of therapy have come with the cost
of both acute and long-term toxicity for children with can-
cer that can interfere substantially with their quality of life.
More than 80% of children undergoing treatment for high-
risk cancer, at some point during their treatment, experi-
ence severe, life-threatening, or fatal toxicity (Fig. 3).
And, for those children who are 5-year survivors, more
than half experience a serious long-term consequence of
their cancer or its treatment. Thus, despite the remark-
able success in the treatment of many children with cancer,
there remains an urgent need to develop more effective and
less toxic treatments for pediatric patients.

**Advances Through Research Collaboration**

Central to the continuous improvement in outcome for
children with cancer have been the collaborative clinical
research efforts throughout the United States, Canada, and
Europe. Pediatric oncology as a subspecialty evolved in

**TABLE 1. US Food and Drug Administration (FDA)
Approval Date for Drugs Most Commonly
Used in the Treatment of Childhood Acute
Lymphoblastic Leukemia**

| DRUG                        | FDA APPROVAL YEAR |
|-----------------------------|-------------------|
| Mercaptopurine (6MP)        | 1953              |
| Methotrexate                | 1953              |
| Prednisone                  | 1955              |
| Cyclophosphamide            | 1959              |
| Vincristine                 | 1963              |
| Thioguanine (6TG)           | 1966              |
| Cytarabine (Ara-C)          | 1969              |
| Doxorubicin                 | 1974              |
| L-Asparaginase              | 1978              |
| Daunorubicin                | 1979              |

*Most drugs were discovered and developed in the 1950s and 1960s; improving the application of these drugs from 1970 through today drove the steady increase in survival in this disease (data from: Hirschfeld S, Ho PT, Smith M, Pazdur R. Regulatory approvals of pediatric oncology drugs: previous experience and new initiatives. J Clin Oncol. 2003;21:1066-1073; and personal communication, Steven Hirschfeld, MD).
Several factors, including the redundant back-office systems and the need for greater collaboration as the molecular underpinnings of childhood cancers divided already rare diseases into even smaller subsets of patients, led in the year 2000 to the voluntary merger of the 4 pediatric groups into a single group: the Children’s Oncology Group (COG).

The evolution of pediatric oncology as a subspecialty, alongside the cooperative group research model, resulted in a remarkably high participation rate of children diagnosed with cancer and their families in clinical trials. Greater than 60% of children newly diagnosed with cancer, and, for young children, close to 90%, participate in clinical research, a figure that readily eclipses the estimated 3% participation of adult patients diagnosed with cancer. This high participation rate has afforded the opportunity to study cancers with an annual incidence of less than 100 cases per year. A primary limitation to participation in clinical trials by children with cancer and their families is the lack of availability of trials at different times in different disease areas. The ability to successfully accrue to clinical trials conducted by the COG is highlighted in Figure 4.

An important offshoot of the high participation in clinical research by children with cancer and the breadth of clinical research conducted is a de facto standardization of treatment for many childhood cancers. Frontline studies, when randomized, contain a standard treatment arm. The standard treatment arms administered in protocols or the most successful arm from prior clinical trials have generally also been adopted as a standard of care for other children with cancer. The net result is that childhood cancer care has become highly standardized relative to other areas of medicine. Improvements in quality and outcome are known to occur through standardization; this has been the focus of several studies, including a comprehensive report by the Institute of Medicine.

FIGURE 4. Annual Accrual to Children’s Oncology Group Clinical Trials by Disease Area. For most childhood cancers, the only time accrual is limiting is when there is no open study, as occurred for non-Hodgkin lymphoma (NHL). ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CNS, central nervous system; NBL, neuroblastoma; STS, soft tissue sarcoma.
The degree to which standardization of care that occurred through clinical research is not known but likely is a contributing factor to the overall improvement in survival outcome for children with cancer.

The cooperative group system funded by the NCI underwent a major restructuring in 2014. The inability to successfully complete several phase 3 clinical trials conducted by the 9 adult cooperative groups was one of the driving factors that led to a series of recommendations by working groups of the NCI and the Institute of Medicine for how to restructure the cooperative group system. The result was the emergence of the National Clinical Trials Network, which consists of 4 adult groups and one pediatric group (COG). For pediatric oncologists, the greatest potential benefit of the new National Clinical Trials Network may be the ability to accrue patients to clinical trials for cancers that cross the pediatric-adult divide. The improvements in outcome for adolescents and young adults have lagged behind (and, in certain cases, significantly behind) the improvements in children. The ability to open clinical trials across the network may help address gaps by increasing enrollment of adolescents and young adults into clinical trials.

**Development of Targeted New Agents for Children With Cancer**

The development of imatinib mesylate (Gleevec; Novartis Pharmaceuticals Corporation, East Hanover, NJ) for the treatment of patients with chronic myelogenous leukemia (CML) ushered in the modern era of targeted therapy. Although CML in children occurs infrequently, one of the most difficult to treat childhood acute leukemias historically had been Philadelphia chromosome (Ph)-positive ALL, which harbors a breakpoint cluster region-Abelson murine leukemia viral oncogene homolog (BCR-ABL) translocation analogous to that found in patients with CML. As results of the significant efficacy of imatinib emerged in early phase adult CML trials, the COG embarked on a relatively rapid series of studies to develop imatinib for children with cancer. Although the efficacy of imatinib in pediatric CML paralleled that observed in adults, the responses observed in children with relapsed or refractory, Ph-positive ALL were relatively short-lived in duration. Given the poor outcome of children with newly diagnosed, Ph-positive ALL after treatment consisting of intensive chemotherapy and, when feasible, by stem cell transplantation, the COG conducted a clinical trial that increasingly integrated imatinib with cytotoxic chemotherapy in children with newly diagnosed, Ph-positive ALL. The ability to successfully integrate this targeted new agent into an intensive chemotherapy background has transformed the outcome for these children, resulting in an estimated 70% ± 6% event-free survival rate at 5 years compared with an historic control rate of less than 30% (Fig. 5).

Since the introduction of imatinib into clinical care, a diverse array of targeted new agents have been developed for adult patients with cancer, and a significant fraction of these target tyrosine kinase-centric or serine/threonine kinase-centric pathways. Selecting from drugs developed for adult cancers (primarily carcinomas) to be developed for childhood cancers remains an ongoing challenge. Nonetheless, new agents targeting the epidermal growth factor receptor pathway, the vascular endothelial growth factor pathway, anaplastic lymphoma kinase, insulin-like growth factor receptor (IGFR), hedgehog signaling, the mammalian target of rapamycin, protein kinase B, γ-secretase, Janus kinase, fms-like tyrosine kinase 3, and other pathways have undergone early phase pediatric testing and, in a select number of cases, are being evaluated in frontline therapies. Several lessons have emerged from the pediatric early phase experience of targeted new therapies that may be generalizable.

**Side-Effect Profile**

Although a frequent limitation of classic cytotoxic chemotherapy is myelosuppression, significant myelosuppression is not a commonly observed adverse effect with many targeted new agents. However, targeted new agents indeed have an adverse effect profile that, in several cases, proves dose limiting. In general, the adverse effect profile observed in children is similar to that observed in adult patients, but the intensity and frequency of toxicities can vary.

One of the early challenges in pediatric drug development for these agents was the need to develop effective management strategies for commonly observed nonmyelosuppressive toxicities. For example, the development of vascular endothelial growth factor inhibitors required a strategy for the management of hypertension that occurs with this class of drugs. For pediatric patients, the NCI Common Terminology Criteria for Adverse Events grading were inadequate for defining toxicities and resultant management strategies. Rather, a paradigm that would quantify pediatric hypertension over the range of normal values observed in children and adolescents, alongside an intervention strategy, was instituted across early phase trials conducted by the COG. Other interventions, including management of rashes frequently observed with several inhibitors, were similarly developed.

**Formulations**

For several small-molecule signal transduction inhibitors, the ability to orally administer drugs, a seeming advantage for adult patients with cancer, creates additional challenges for pediatric drug developers. Many of the small-molecule
inhibitors recently developed are highly insoluble, making the development of a liquid formulation for young children difficult. Successful development of a liquid formulation also requires additional clinical trial investigations, including determining the bioavailability of the liquid formulation relative to the solid (tablet, capsule) formulation. For drugs that have limited bioavailability in adult patients, a small adult clinical trial defining the relative bioavailability is often required, because a significant difference in bioavailability could present an increased risk for children participating in early phase trials. In general, however, the primary difference observed between formulations has been an earlier and higher peak concentration with liquid formulations compared with pill/capsule formulations, with similar overall drug exposures.27

Dependency on Adult Drug Development Plans

An additional lesson learned from pediatric early phase development of targeted new agents is not a new lesson but a distressingly old lesson: dependency of pediatric drug development on the adult drug development program. The most recent example is with the development of IGFR-1 inhibitors. Almost 30 candidate drugs targeting IGFR-1 were tested in more than 70 clinical trials conducted in a range of cancers.42 One of the most consistent signals observed occurred in patients with relapsed Ewing sarcoma, in which single-agent response rates approximating 10% were observed.43–46 A major area of development for IGFR-1 inhibitors, however, was for adult patients with nonsmall cell lung cancer and other carcinomas. Two pivotal, randomized, phase 3 trials were closed early for lack of efficacy, and a third randomized trial was cancelled.42 These and other negative trials in adult cancers led to an exodus of IGFR-1 development by the biopharmaceutical sector that prevented planned randomized clinical trials in pediatric patients with Ewing sarcoma. After several years of delay, a partnership between the NCI and one sponsor was ultimately developed to allow for continued pediatric evaluation of an IGFR-1 antibody in patients with Ewing sarcoma by the COG.

Defining the Target

It is estimated that the biopharmaceutical industry funds approximately 60% of all biomedical research conducted in the United States, with federal sources (e.g., the National Institutes of Health) accounting for approximately 25% of overall funding.47 This overall investment distribution, however, does not translate down to investment in childhood cancer research, which depends almost entirely on public sources of funding. Not only is there limited investment by the private sector in childhood cancer drug development in clinical research, but there is virtually no investment in pediatric preclinical research. This directly impacts the extent of knowledge of target identification for childhood cancers available to investigators planning for and prioritizing new agents in the clinical development pipeline.

In the United States, the NCI has supported 2 programs to help bridge knowledge gaps in target identification and

FIGURE 5. Long-Term Outcome of Children Treated on Children’s Oncology Group (COG) Study AALL0031. The study incorporated imatinib mesylate into a high-risk chemotherapeutic regimen for children with Philadelphia chromosome-positive acute lymphoblastic leukemia relative to historic controls who did not receive this targeted new drug (data from: Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a Children’s Oncology Group study. J Clin Oncol. 2009;27:5175-5181; Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children’s Oncology Group study AALL0031. Leukemia. 2014;28:1467-1471; and personal communication, Steven Hunger, MD).
new drug development. The first program is the Pediatric Preclinical Testing Program (PPTP), which comprises a consortium of investigators to evaluate new agents with in vitro and in vivo models, primarily focusing on human tumor xenografts. The PPTP studies a limited number of new agents that are in clinical development for adult cancers in a range of well-characterized pediatric cancer models. The PPTP has studied a breadth of new agents, and its data have impacted the prioritization of agents to be studied in the clinic. In several aspects, however, the program is a continuing experiment, and its ultimate impact on childhood cancer drug development is not yet defined.

The NCI Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program is molecularly characterizing several high-risk childhood cancers, including subtypes of ALL, AML, neuroblastoma, osteosarcoma, and select kidney tumors. The TARGET program is the collaborative effort of a consortium of extramural and NCI investigators along with members of the COG. The consortium uses various sequencing and array-based methods to examine the genomes, transcriptomes, and epigenomes of select childhood cancers. Several important findings have emerged from the TARGET program, perhaps most notably the definition of a high-risk subtype of childhood ALL. A subgroup of children with high-risk ALL have Ph-like ALL, which is characterized by a gene-expression profile similar to that of BCR-ABL1-positive ALL, alterations of lymphoid transcription factor genes, and a poor outcome. Ph-like ALL is characterized by a range of genomic alterations that activate a limited number of signaling pathways, several of which may be amenable to inhibition with approved tyrosine kinase inhibitors. On the basis of these findings, the COG will be initiating a clinical trial that identifies these children near the time of their diagnosis and, when appropriate, will evaluate the impact of integrating a targeted new drug with chemotherapy for patients with Ph-like ALL.

Significantly more translational research is needed to better define the molecular targets across the spectrum of childhood cancers. Currently, only a limited number of diagnoses or subsets of diagnoses are likely to benefit from the current generation of targeted new agents, several of which are being actively pursued in both proof-of-principle and frontline clinical trials.

Global Regulatory Initiatives

Childhood cancers are a group of rare and ultrarare diseases. As such, successful economic models for the biopharmaceutical industry to develop drugs for childhood cancer have proven elusive. Without appropriate incentives and regulations, childhood cancer drug development would lag increasingly further behind adult cancer drug development. The problem is not limited to childhood cancer drug development but, in fact, impacts drug development for a range of pediatric diseases and conditions. In the United States, the first successful legislative approach to begin addressing this problem was enacted in 1997 through the FDA Modernization Act (FDAMA). FDAMA provided an additional 6 months of marketing exclusivity incentive to industry and catalyzed the development and conduct of a range of pediatric clinical investigations. FDAMA and the incentive, coupled with the Pediatric Final Rule (the requirement), were subsequently replaced by the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), now in place for a more than a decade. An Institute of Medicine report on BPCA and PREA found that important information to guide clinical care for children was emerging from these studies and noted a trend in improvement in the quality of studies and reporting of results over time. Based in part on the US experience, in January 2007, the European Union (EU) adopted the EU Pediatric Regulation, which introduced several obligations and incentives for pharmaceutical companies. Central to the EU Pediatric Regulation are the development of Pediatric Investigation Plans (PIPs), a process overseen by the European Medicines Agency’s Pediatric Committee.

For childhood cancer drug development, the most notable impact of the US and EU legislative initiatives has been the increasing engagement of the biopharmaceutical industry with investigators from academia in planning for pediatric drug development. One limitation of current initiatives, however, has been the issuance of waivers to conduct pediatric clinical trials. The requirement to conduct pediatric studies on both sides of the Atlantic is directly linked to the specific drug indication approved for adult patients. Although the mechanism of action of a new drug may be relevant for pediatric cancers, if the primary indication for the drug in adults essentially does not occur in children (eg, colon cancer, lung cancer), then a waiver is issued. Thus, in the United States, PREA requirements rarely apply to cancer drugs, and only the incentive (BPCA) is operative. Efforts in Europe are underway to try to address the issue of waivers within the PIP framework.

Although the intent of these initiatives has been clear, there have also been some unexpected and unwelcome effects on childhood cancer drug development. One such issue has been a paradoxical delay in starting select, early phase trials for children with cancer, because industry sponsors can be reluctant to begin clinical development without final approval for a PIP from the European Medicines Agency’s Pediatric Committee. Because PIPs detail phase 1, 2, and 3 development, such plans can be both onerous and, in terms of phase 3 trial plans, quite speculative.

The major underlying issue with current regulatory requirements, however, is that, by definition, the requirements are...
drug-centric and not disease-centric. Regulatory authorities are not in a position to prioritize one drug over another for the treatment of any specific childhood cancer. Rather, the focus of regulatory programs is restricted to development plans for specific drugs, resulting at times in competing studies of different drugs for the same, rare population of patients. Prioritization of studies is complex and should not be relegated to industry sponsors and regulatory agencies.

Solutions to this conundrum are an ongoing area of discussion among stakeholders. It is important to note that most of the current US and European regulatory initiatives focus on leveraging drugs developed for adult cancers to see whether and how best to develop a subset of these agents for pediatric malignancies. The fact that there were no initiatives for the biopharmaceutical industry to develop a first-in-children cancer drug was the impetus behind the 2011 US legislative incentive: the Creating Hope Act, which provides an incentive to industry sponsors who develop a new drug for life-threatening illness as a first-in-children indication. The incentive takes the form of a priority review voucher at the FDA that can be applied to another drug. In 2014, the first voucher, which was issued for the development of a treatment of children with Morquio A syndrome (part of a group of diseases called mucopolysaccharidosis in which the body cannot break down glycosaminoglycans), was sold for $67.5M, providing proof of principle of an economic incentive for the biopharmaceutical industry that may positively impact the development of new drugs for children with cancer.

Future Directions

Despite the remarkable advances that have resulted in children with cancer having an approximate 80% overall chance of 5-year event-free survival, childhood cancer remains the leading cause of death from disease in children in the United States, and treatment-related morbidity and mortality remain substantial problems both during therapy and well into survivorship. Targeted new agents hold the prospect for more effective and less toxic treatment; however, to date, only limited numbers of children with cancer, including children with anaplastic large cell lymphomas and subsets of children with ALL, appear likely to derive significant long-term benefit from the current generation of targeted new agents, with active investigation ongoing for children with AML, neuroblastoma, Ewing sarcoma, medulloblastoma, and other subsets of cancer. The exciting prospects for cellular therapy and immunotherapy, which have been highlighted with new agents including blinatumomab and chimeric antigen receptor-modified T cells for children with CD19-expressing B-lineage lymphoblastic leukemia, are poised to add highly effective new therapeutic modalities to the pediatric oncology portfolio.

The collaborative research infrastructure for children with cancer is well positioned to continue to advance novel treatments into clinical investigations for a spectrum of rare and ultrarare childhood cancers. As our understanding of the molecular basis of childhood cancers continues to increase, there will be greater need for global collaboration in pediatric clinical-translational oncologic research, because the already small populations of children diagnosed with specific cancers will be further divided into smaller subpopulations.

More effective alignment between the biopharmaceutical industry, global regulatory agencies, academic investigators, and other stakeholders (including, of course, patient families) is needed. Legislative efforts have made a modest impact on childhood cancer drug development, but significant refinement in several areas is needed. A greater investment of resources in target discovery and validation can help drive much needed development of new, more effective treatments for children with cancer and afford them not only cures but cures free of the too often lifelong burden of current-day cancer treatments.

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