History of Drug Development for Children with Cancer

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1.1 Introduction

It has been said that the profound improvement in the treatment and resulting overall outcomes of children with cancer represents one of the greatest achievements and success stories in all of medicine. As a result of decades of experimental approaches to the treatment of children pursued through clinical trials designed and conducted by dedicated scientists and clinicians, the willingness of children and their parents to participate in clinical research, the extraordinary increase in understanding the biologic basis of cancer, and the increasing ability to design therapies to target specific biologic processes, four out of five children diagnosed with cancer can now be cured of their disease (Smith et al. 2014; Howlander et al. 1975–2017). And in the most common childhood cancer, acute lymphoblastic leukemia (ALL), cure rates have risen to highs of 90–95% (Hunger and Mulligan 2015) (Fig. 1.1). Despite the impressive accomplishment, too many children experience recurrence of their disease during or upon completion of primary therapy, present with metastatic disease at diagnosis, or are inflicted with especially recalcitrant cancers and fail to experience favorable long-term outcomes. In addition, the

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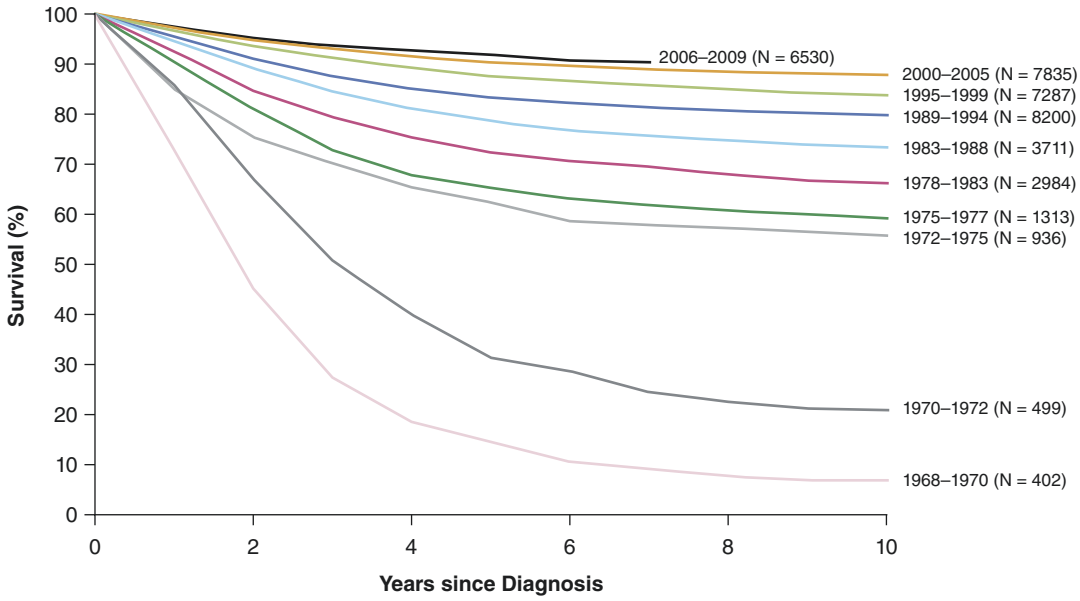

Fig. 1.1 Overall survival among children with acute lymphoblastic leukemia (ALL) who were enrolled in Children's Cancer Group and Children's Oncology Group clinical trials, 1968–2009. (Reproduced with permission)

cost of successful cancer therapy in terms of long-term or late-occurring toxicities associated with treatment provides a sobering reality to the successes achieved and provides the impetus for the search of optimally efficacious and safe therapeutic options for children with cancer.

In 2010, Siddhartha Mukherjee published the book *The Emperor of All Maladies,* a landmark achievement in the history of medicine (Mukherjee 2010). This elegantly written book is a self-described "biography" of cancer drug discovery and development. Interested readers are encouraged to read this complete history that traces therapeutic approaches from ancient to modern times. Instead of a similarly complete and epic tome on the scale of Mukherjee's book, this short chapter will instead focus on the advent of cancer chemotherapy from Sidney Farber's seminal investigations in the 1940s.

1.2 Initial Progress

By the 1930s, it was increasingly recognized that the use of surgery, pioneered in the nineteenth century, and radiation, pioneered in the early twentieth century, to treat cancer was limited to the local control of tumor masses, with neither effective in the treatment of children with leukemia. This led to the Roosevelt administration's passage of the National Cancer Institute Act of 1937 that created the National Cancer Institute (NCI) whose mission was to coordinate cancer research and education. In 1944, the NCI became a part of the National Institutes of Health (NIH).

In 1947, Sidney Farber used an antimetabolite, the antifolate, aminopterin, to first treat a child with leukemia (Fig. 1.2). His seminal work was based on George Minot's scientific work on B_{12} deficiency in patients with pernicious anemia and Lucy Mills identification of folic acid as essential for cell division in patients with nutrition-related anemias. Between 1948 and 1952, Farber's use of methotrexate to treat children with leukemia resulted in a median survival of 8 months, in striking contrast to median survivals of 1–3 months prior to Farber's experimental approach. The addition of purine antagonists, mercaptopurine, to these antifolates further increased the median survival to 1 year by the mid-1950s.

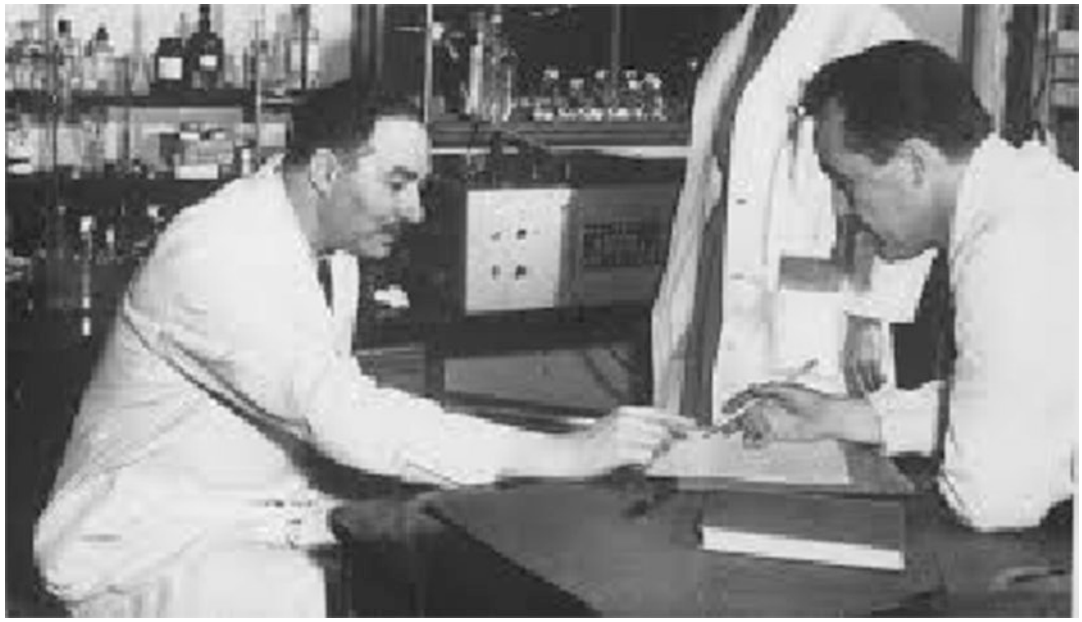

Fig. 1.2 Sidney Farber

1.3 Rise of the Cancer Cooperative Groups

Given the rarity of leukemia and other cancers in children, and the recognition of the need to work collaboratively across multiple institutions, the concept of cooperative groups emerged from the work related to the investigational approach to pediatric leukemias, and later several adult cancers. This led to the establishment of the Cancer Chemotherapy National Service Center at the NIH in 1955 (O'Leary et al. 2008). This innovative and paradigm shifting group had as its primary mission to study antileukemia agents in children. The clinical trials developed by this group were conducted by the Acute Leukemia Chemotherapy Cooperative Group A (ALCCSGA). The ALCCSGA initially included eight member sites, all children's hospitals, and pediatric cancer programs. The cooperative group's first clinical trial was a comparison of 6-mercaptopurine versus 6-mercaptopurine plus azaserine (Heyn et al. 1960). In 1958, Emil Frei, Emil Freireich, and James Holland at the NCI performed combination chemotherapy trials for children with leukemia testing 6-mercaptopurine plus methotrexate. The ALCCSGA also initiated phase I clinical trials in children to test a number of drugs, including mitomycin C, 5-fluroro-2′-deoxyuridine, and actinomycin D. The development of the Acute Leukemia Group B followed shortly thereafter and later became the Cancer and Leukemia Group B (CALGB).

By 1959, the ALCCSGA had grown to 12 member institutions. The ALCCSGA would eventually become the Children's Cancer Study Group (CCSG), subsequently renamed the Children's Cancer Group (CCG). In 1956, the Southwest Cancer Chemotherapy Study Group (SWCCSG) was founded to study leukemia in children and adults. The SWCCSG was later renamed the Southwest Oncology Group (SWOG), and its pediatric division merged with that of the CALGB to become the Pediatric Oncology Group (POG). Together, the CCG and POG conducted 693 treatment studies in children with cancer. In 2000, the CCG and POG, along with the NCI's smaller disease-specific pediatric oncology cooperative groups, the International Rhabdomyosarcoma Study Group (IRSG) and the National Wilms Tumor Study Group (NWTS) merged to become the Children's Oncology Group (COG). Currently, the COG is the world's largest organization devoted to clinical, translational, and epidemiological research in childhood cancer, having conducted 270 treatment studies and 551

nontreatment studies (i.e., supportive care, screening, biology, specimen acquisition, and data analysis studies) since its inception.

1.4 Impact of Regulation to Improve Safety and Efficacy Federal Laws Providing a Regulatory Framework for Drug Development in Children

Unfortunately, catastrophic events and deaths in children from unsafe medicinal products led to the need for a series of laws and a system of regulations to ensure the safety and efficacy of drugs approved for use in children. These US laws, and the regulations that emerged in other parts of the world, and their impact on pediatric cancer drug development are detailed in Chap. 10.

The first of these addressed the adulteration of medicinal products. The Drug Importation Act of 1848 was passed after the blistering agent, Spanish flies (cantharides), was found to be adulterated with other insects and beads (Fig. 1.3). Early legislation addressing the safety of medicinal drug products included the Biologics Control Act of 1902 that was passed after the death in 1901 of a child from tetanus after treatment with a diphtheria antitoxin preparation. The Pure Food and Drugs Act of 1906 was passed after the deaths of a number of infants who were given Mrs. Winslow's Soothing Syrup that was intended to treat teething pain and colic. This product did not divulge its ingredients that included morphine (Fig. 1.4). In 1937, there was another tragedy involving a product known as elixir of sulfanilamide, manufactured by the S.E. Massengill Company in Bristol, Tennessee (Fig. 1.5). It was marketed as a "treatment of all conditions in which the hemolytic streptococci appear." It was marketed, in part, directly to children since the very insoluble sulfanilamide was dissolved to generate a liquid formulation thought to be appropriate for pediatric use. More than 100 people died, the majority being children, due to the highly toxic chemical diethylene glycol that was used as the solvent. Public outcry helped to facilitate the Roosevelt administration in its passage of the Food, Drug, and Cosmetic (FDC) Act of 1938 that gave the Food and Drug Administration (FDA) the authority to approve drugs that were proven safe. However, 1962 saw another devastating tragedy, again involving children, who were born with phocomelia, a severe

Fig. 1.3 Cantharides (Spanish flies)

Fig. 1.4 Mrs. Winslow's Soothing Syrup

Fig. 1.5 Elixir sulfanilamide

congenital condition of upper and/or lower limb deformities resulting from their pregnant mother's use of the sedative, thalidomide, to treat morning sickness. In response, the Kefauver-Harris Amendment of 1962 was passed that provided a framework for drug manufacturers to prove that their products were not only safe but also effective.

In 1997, the Food, Drug, and Cosmetic Act was amended as the Food and Drug Administration Modernization Act (FDAMA) which provided 6 months of marketing exclusivity as an incentive to manufacturers who voluntarily conducted studies of drugs in children. In 2003, the Pediatric Research Equity Act was passed, following the rescinding of the Pediatric Rule to require pediatric assessments of new drugs when the clinical indications for which the drugs were developed existed in children and the drugs were likely to be used in the pediatric population. In 2002, the exclusivity provision released as part of FDAMA was reauthorized as the Best Pharmaceuticals for Children Act (BPCA). For various reasons, it is perhaps useful to view the FDA's approval of drugs that include a pediatric indication before, and after, passage of the FDAMA (Tables 1.1 and 1.2).

Table 1.1 Drugs with an indication for children with cancer, approved by the FDA prior to FDAMA

Drug	Initial pediatric approval	Currently approved indications
Mercaptopurine	1953	ALL
Methotrexate	1959	ALL, meningeal leukemia, OS, NHL
Cyclophosphamide	1959	Leukemia, lymphoma, NBL, retinoblastoma
Vincristine	1963	ALL, lymphomas, WT, RMS, NBL
Dactinomycin	1964	ES, sarcoma botryoides
Vinblastine	1965	HL, histiocytosis, testicular germ cell carcinoma
Thioguanine	1966	AML
Cytarabine	1969	AML
Procarbazine	1969	HL
Doxorubicin	1974	WT, NBL, STS, HL, other lymphoma, ALL, AML
Lomustine	1976	Brain tumors, HL
L-Asparaginase	1978	Leukemia
Daunorubicin	1979	ALL
PEG-asparaginase	1994	ALL
Tretinoin	1995	APML
Teniposide	2002	Refractory ALL

ALL acute lymphoblastic leukemia, *OS* osteosarcoma, *NHL* non-Hodgkin's lymphoma, *NBL* neuroblastoma, *WT* Wilms' tumor, *RMS* rhabdomyosarcoma, *ES* Ewing sarcoma, *HL* Hodgkin's lymphoma, *AML* acute myeloid leukemia, *STS* soft tissue sarcoma, *APML* acute promyelocytic leukemia

Table 1.2 Drugs with an indication for children with cancer, approved by the FDA after FDAMA

Drug	Initial pediatric approval	Currently approved indications
Arsenic trioxide	2000	APML
Clofarabine	2004	Refractory ALL
Nelarabine	2005	T-cell ALL
Erwinia asparaginase	2011	ALL
Everolimus	2012	SEGA
Denosumab	2013	Giant cell tumor of the bone
6-Mercaptopurine oral solution	2014	ALL
Dinutuximab	2015	High-risk NBL
Pembrolizumab	2017	Refractory classical HL
	2017	MSI-H- or MM repair-deficient solid tumor
	2018	Refractory primary MLBCL
	2018	Metastatic Merkel cell carcinoma
	2020	Refractory classical HL
	2020	Mutational burden-high solid tumors
Avelumab	2017	Metastatic Merkel cell carcinoma
Gemtuzumab	2017	R/R CD33+ AML
	2020	Newly diagnosed CD33+ AML
Tisagenlecleucel	2017	R/R ALL
Dasatinib	2017	Ph + AML in chronic phase, Ph + ALL
Imatinib	2017	Ph + ALL, Ph + CML
Ipilimumab	2017	Unresectable or metastatic melanoma
Nilotinib	2018	Ph + CML in chronic phase
Emapalumab	2018	R/R primary HLH
Larotrectinib	2018	Solid tumors with NTRK gene fusion
Tagraxofusp	2018	BPDCN
Calaspargase	2018	ALL
Entrectinib	2019	Solid tumors with NTRK gene fusion
Naxitamab	2020	R/R NBL
Tazemetostat	2020	Metastatic or locally advanced epithelioid sarcoma
Pralsetinib	2020	RET-mutated medullary thyroid cancer
Selpercatinib	2020	RET fusion-positive thyroid cancer
Selumetinib	2020	NF1, inoperable plexiform neurofibromas
Crizotinib	2021	R/R ALCL
Asparaginase erwinia chrysanthemi	2021	ALL, lymphoblastic lymphoma

APML acute promyelocytic leukemia, *ALL* acute lymphoblastic leukemia, *SEGA* subependymal giant cell astrocytoma, *NBL* neuroblastoma, *HL* Hodgkin's lymphoma, *MSI-H* microsatellite instability-high, *MM* mismatch, *MLBCL* mediastinal large B-cell lymphoma, *AML* acute myeloid leukemia, *CML* chronic myeloid leukemia, *HLH* hemophagocytic lymphohistiocytosis, *BPDCN* blastic plasmacytoid dendritic cell neoplasm, *ALCL* anaplastic large cell lymphoma

Although PREA and BPCA resulted in the addition of pediatric use language in product labeling of more than 800 drug products since the passage of these respective pieces of legislation, the contribution of these laws to cancer drug development was due solely to BPCA; no cancer drug has been subject to a PREA-mandated study since the requirement is indication-based and most cancers seen in adults rarely, if ever, occur in children. In those rare situations where diseases span the adult and pediatric populations, the orphan disease designation exempts the sponsor from the PREA requirement. This unintended oversight has been finally and recently addressed by the RACE (Research Acceleration for Cure and Equity) for Children Act, incorporated as part of the Food and Drug Administration Reauthorization Act (FDARA) passed in 2017. Section 504 of FDARA amends Section 505B of the FD&C Act to authorize

FDA to require early pediatric assessment of new cancer drugs developed for cancers in adults when the molecular target to which that drug is directed is substantially relevant to the growth or progression of a cancer that occurs in children. The impact of this new law on the regulatory environment for pediatric cancer drug development nationally and global is discussed in Chap. 10.

1.5 Indications

The historical paradigm resulted in the approval of 16 cancer drugs prior to 1997 for children with a cancer indication (Table 1.1), with 28 drugs approved since 1997 (Table 1.2). The first cancer drug approved by the FDA for children with cancer was 6-mercaptopurine, approved in 1953 for children with ALL. Looking at all 44 drugs that are approved by the FDA for various pediatric cancer indications, the vast majority are for children with hematologic malignancies (n = 37 indications) with fewer drugs approved for solid tumor indications (n = 24 indications). Sixteen FDA-approved therapies have ALL as an indication, with four for acute myeloid leukemia (AML), two for acute promyelocytic leukemia (APML), two for chronic myeloid leukemia (CML), seven for various forms of non-Hodgkin's lymphoma (NHL), five drugs for Hodgkin's lymphoma, and one for blastic plasmacytoid dendritic cell neoplasm (BPDCN).

Despite significant effort and numerous clinical trials, there are fewer approved drugs for children with solid tumors, with the largest number (n = 4) for children with neuroblastoma. For other solid tumors, there are only small numbers of approved drugs. Disappointingly, most of these drugs are quite old. For example, only one drug, vincristine, is approved for the treatment of children with rhabdomyosarcoma, with this approval in 1963. Similarly, there is only one drug, dactinomycin, approved for the treatment of children with Ewing sarcoma, with this approval in 1964. However, dactinomycin is no longer a component of standard of care for children with Ewing sarcoma.

Interestingly, and consistent with the great advances in the biology of cancer in children and adults, six drugs have recently been approved based on a biologic target that is largely "agnostic" of the organ of origin. These drugs are directed at several interesting biologic targets, including RET, NTRK, microsatellite instability, mismatch repair deficiency, and tumor mutational burden. In addition, the development of more novel agents like the chimeric antigen receptor T-cell (CAR-T) product tisagenlecleucel received its initial approval for a pediatric oncology indication (i.e., relapsed or refractory ALL).

1.6 Summary

Since its inception, the FDA has approved only 44 drugs for children with cancer, in striking contrast to more than 600 drugs for adults with cancer. Despite this difference, it is clear that the development of new therapies for children with cancer has, in large part, driven the process of investigating the safety and effectiveness of all cancer drugs. Notably, the development of chemotherapy approaches was pioneered by Farber's work in children with ALL along with that of Frei, Holland, and Freireich; the first cooperative cancer group was focused on children with ALL; and most significant laws at ensuring the safety and efficacy of new drugs were in response to injury and deaths in children exposed to unsafe and ineffective products. It can also be argued that the first "targeted" therapy (L-asparaginase) was developed and approved for children with ALL. L-Asparaginase targets a specific molecular target, the amino acid asparagine, which is essential for the survival of acute lymphoblastic leukemia cells.

With the remarkable advances in science and insights into the biology of these cancers, it is anticipated that an increasing number of innovative drug products and biologics will be developed and approved in the future. But unique to the assessment of success in the treatment of children with cancer is not only cure of their cancer but more accurate assessments of excess risk of death that is the result of increased lifetime morbidity and mortality.

It is known that survivors of childhood cancer have an increased risk of death due to cardiac disease, pulmonary disease, new cancers, and a number of chronic health conditions (Begg and Schrag 2002; Mertens et al. 2008, 2015; Williams et al. 2021). The future of pediatric cancer therapy development will therefore require not only more effective cancer treatments but, critically, less toxic therapy.

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