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Conquering the Cancer Care Continuum™

Pediatric Cancer Care

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There is nothing that pulls at my heart strings more than the sight of a young child dealing with a diagnosis of cancer. This issue of *Conquering the Cancer Care Continuum*™ focuses on pediatric cancer care, a challenging area of oncology management, but one in which amazing progress is being made. As discussed in the oncology pharmacist perspective, 2 important trends are paving the way for improved clinical outcomes in children with cancer. These are the identification of genetic polymorphisms that affect the way in which patients metabolize certain drugs, and an increase in pharmacogenomic screening, which can be used to identify driver mutations that are likely to respond to specific therapies. The oncology nurse perspective provides a brief history of pediatric oncology, including the high mortality rates that were so common decades ago, and explores promising advances in treatment. Finally, the physician perspective discusses effective strategies for curing cancer in more children in low- and middle-income countries.

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Although certainly there are still children and teenagers dying from specific malignancies, fortunately, there are more surviving than ever before. In fact, the very high survival rate in pediatric leukemia is probably the greatest success story in the field of hematology/oncology. With the availability of targeted therapies, we have entered a new era that provides hope for children diagnosed with other types of cancer. However, along with our ability to save more young patients, we are faced with ongoing challenges that need to be addressed, including lingering adverse events and late effects of treatment. Unfortunately, we are uncertain as to what the late effects of some treatments will be, as they have been used in practice for a relatively short period of time.

We are also witnessing an increase in the availability of clinical trials for children with cancer, which is very good news. Children who have achieved remission are typically monitored by pediatric oncology survivorship clinics. A great deal has been learned through this follow-up, which goes on for many decades after treatment. This will remain an important strategy as new drugs and combination regimens continue to be integrated into the treatment paradigm. Clinical trials of various approaches to survivorship management will also be highly important.

As you read this issue, you will have the opportunity to consider what the experience is like for a young

TEVA Oncology

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patient coping with cancer treatment. Hair loss is perhaps the most obvious sign to a child that something very serious is happening inside of his or her body. Although individuals are often focused on the immediate effects of treatment, pediatric oncologists must look beyond the present and consider future life goals of their patients. For example, there is a need for timely fertility preservation (even for patients in their late 30s and early 40s); limited use of drugs that cause peripheral neuropathy, which may interfere with career goals; and treatments that prevent the body from rapidly aging, which occurs when a person's body is stripped of its sex hormones. And there is that gray area in which young adults are diagnosed with a childhood cancer and need to decide if they will be managed by a pediatric oncologist or an adult oncologist. That is all the more reason for those of us who are oncology providers to look beyond the pathology of our patients and factor into the treatment plan their known or likely life goals.

We can apply much of what we learn from pediatric oncology survivors to adult survivors, recognizing that adults are living longer—many decades after their treatment was completed. My hope is that the concepts discussed in this issue will help you in the care of your patients with cancer regardless of their age. ■

Acute Lymphoblastic Leukemia in Childhood: A Nurse's Perspective

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The birth of the pediatric hematology/oncology specialty can be traced back to the early part of the 20th century, when pediatricians began describing hematologic abnormalities in infants and children. Although hematologic diseases were regularly studied and diagnosed in this era, childhood cancer was still considered a rare phenomenon and received little attention in medicine. The first textbook dedicated to pediatric oncology was published in 1940 and stated that the average survival for a child diagnosed with acute lymphoblastic leukemia (ALL) was shorter than 3 months.[1] Seven years later, Sidney Farber, MD, a pathologist at Boston's Children's Hospital, founded the Children's Cancer Research Foundation and set out to cure childhood ALL. At that time, the only therapy available to treat the disease was cortisone, which could offer only a temporary reduction in leukemic cells. Building on the understanding of how folic acid interacts with bone marrow function, Dr Farber began treating children diagnosed with ALL with a purine antagonist. With this approach to treatment, he was able to induce remission in a majority of patients with ALL, but the remissions were not sustainable, and relapse resulting in death was common.[2]


Kathy Ruble, RN, CPNP, PhD

Dr Farber's discovery led to the proliferation of antileukemic drugs in the 1960s, including vinca alkaloids and cytotoxic agents, which remain the backbone of therapy for ALL. Animal models of leukemia had come into play by this time, with Howard Skipper, MD, showing that combining drugs with different mechanisms of action could theoretically cure leukemia.[3] By 1965, the National Institutes of Health reported that the use of multidrug therapy led to superior results in the treatment of patients with ALL.[4] During this same time period, the recognition of sanctuary sites and their association with disease relapse was under investigation and ultimately led to the addition of radiation and intrathecal chemotherapy to treatment regimens.[5] Survival rates improved dramatically with these comprehensive treatments. By 1990-1994, the 5-year survival rate for childhood ALL reached 83.7%, and in the period 2000-2005, a mere 65 years after ALL was declared a nearly universally fatal disease, the 5-year survival rate was 90.4%.[6] As the survival time for childhood ALL began to lengthen, the sequelae of therapy began to surface. By the mid-1970s, late effects of the treatment of childhood cancer began to emerge in the literature. Leukemia researchers began to consider the long-term effects of treatment when designing treatment protocols. For example, crucial research on the impact of cranial radiation on long-term neurocognitive impairment has led to decreasing doses of cranial radiation, from 2400 cGy in early therapies to 1200 to 800 cGy in subsequent cohorts.[7]

The next challenge for researchers was modifying therapies to lessen the risk of long-term complications while maintaining high cure rates. To achieve this goal, investigators looked to risk factors for resistant disease among patients. The ability to identify those who were at lowest risk of relapse and delivering less intense therapies to this group would decrease the number of survivors with significant late effects. Initial risk factors included the most basic clinical characteristics such as age, white blood cell count, race, and sex. As laboratory research techniques became more sophisticated, it was obvious that there were many more

Leukemia researchers began to consider the long-term effects of treatment when designing treatment protocols.

molecular and genetic risk factors associated with poorer outcomes in children with ALL. For example, childhood ALL that is associated with a Philadelphia chromosome mutation has consistently had poor survival and has warranted some of the most intense therapies, including bone marrow transplantation. Currently, the ability to perform whole-genome sequencing of leukemic cells means that nearly every child with ALL has a known, specific genetic abnormality associated with their leukemia, and there are at least 15 genetic abnormalities associated with this disease.[8]

Recently, a subpopulation of patients with refractory ALL was found to have mutations of genes encoding cytokine receptors and regulators of kinase signaling.

The most exciting progress that has occurred as a result of advances in genetic classification and diagnosis of childhood ALL is the potential for the development of targeted therapies. Recently, a subpopulation of patients with refractory ALL was found to have mutations of genes encoding cytokine receptors and regulators of kinase signaling.[9] Soon there were anecdotal reports in the literature of patients with refractory childhood ALL associated with this mutation who were subsequently treated with tyrosine kinase inhibitor drugs and achieved remission.[10,11] This promising, targeted therapy is quickly changing the landscape for children with Philadelphia chromosome–positive ALL. According to a recent report published in the journal *Cancer*, the 5-year event-free survival rate for children with this mutation treated with a tyrosine kinase inhibitor in addition to traditional chemotherapy was 68.6%, compared with 31.6% for those who did not receive this drug.[12]

What lies ahead for children diagnosed with ALL? Well, I certainly do not have a crystal ball, but I have to say the future looks quite bright. Clinical trials are abundant, and if the historical pace of advances is any indication, more effective agents and combinations are likely to drive the cure rates of childhood ALL even closer to 100% while decreasing the long-term complications of treatment. Perhaps there will be a day in the not-so-distant future when targeted therapies will be developed for all of the most challenging childhood cancers and we can finally bring this devastating disease to its knees. ■

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Pediatric Cancer Care: A Pharmacist's Perspective

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As a practitioner in adult oncology, it is only on rare occasions that I see pediatric patients managed in our clinic. Generally speaking, such patients seen in this setting are mid-adolescents with diagnoses of Hodgkin lymphoma who are being treated with a standard adult regimen. These patients are presented with the option of being treated at the local children's hospital or our cancer center, and those who choose the latter usually do so because they more closely identify with our adult patient population than with the young children they see at the facility down the street. However, a conscious choice to receive cancer therapy among adults does not an adult patient make for these adolescents who are younger than 20 years of age. Because of the age and the stage of maturation and physical development, there are issues that must be addressed in this patient population that are generally irrelevant for the majority of our adult patients with cancer. These situations frequently require that we "think outside of the box" of our standard protocols to address issues such as fertility preservation, hair loss, and issues related to drug dosing, supportive care, and therapeutic monitoring, which may vary greatly from the persons 50 years of age and older who constitute the majority of patients treated in our setting each day.

Steve Stricker, PharmD, MS, BCOP

Certain themes that are gaining traction in the management of older adults diagnosed with cancer are often important for younger patients as well. These similarities are the starting point for identifying the common ground that provides us some element of assurance in knowing that we are providing the best possible care for our patients even while we are admittedly out of our comfort zone. Two of these areas in particular involve the concepts of identifying genetic polymorphisms related to individual drug metabolism and the use of pharmacogenomic screening to identify likely driver mutations that may be specifically targeted with certain drugs.

Advances in managing childhood cancers are one of the great success stories in our collective history of oncology care. We now see an overall cure rate of nearly 80% for the most common pediatric malignancies.[1] This pattern is both a reflection of the use of more aggressive cytotoxic chemotherapy regimens (compared with adult regimens) and also of the natural resilience of children. Although success rates are one of the best measures of how far we have come in treating childhood cancers, patient tolerance should also be closely monitored, just as it is in adult patients. One intersection of drug tolerance and science was identified when it was recognized that certain pediatric patients with acute lymphoblastic leukemia (ALL) were more susceptible to specific adverse events, including a significantly higher incidence of febrile neutropenia associated with exposure to some purine analogs. The role of thiopurine S-methyltransferase gene polymorphisms was discovered to affect the serum concentration of active drug via inhibition of drug metabolism. The increased area under the curve that results from this low enzymatic activity has been clearly demonstrated to affect the incidence of adverse events, drug tolerance, and quality of life.[2] Similar outcomes have been observed with individualizing doses of other commonly utilized drugs as well, based on the patient's ability to clear the drug.[3] Although these older pharmacogenetic approaches that focus on single-gene polymorphisms and their associated genotypic and phenotypic expression have been highly successful, the future more likely lies in the use of wholesale pharmacogenomic screening to identify actionable driver mutations in individual patients.

We now see an overall cure rate of nearly 80% for the most common pediatric malignancies.

Much has been written in the past decade on the concept of driver versus passenger mutations and their relative contributions in human cancers. Daniel A. Haber, MD, PhD, Director of the Massachusetts General Hospital Cancer Center, has written extensively on this topic and defines driver mutations as exerting "selective pressure during tumorigenesis" versus passenger mutations, which he defines as incidental genetic abnormalities.[4] The next-generation approach of Foundation Medicine in Cambridge, MA, builds upon this pioneering work in cancer biology to create a genomic profile from the tumor's DNA. It is important to recognize that rather than screening for specific genetic polymorphisms, as described for children with ALL treated with specific drug therapy as discussed above, Foundation Medicine seeks to understand the role that known genetic abnormalities may play in cancer types where they are not commonly expected or found. Because many pediatric cancers do not share the number of available treatment options found in adult oncology, utilization of the Foundation Medicine approach for the youngest of cancer patients makes sense.

Given the paradigm shift that is gradually occurring toward targeted therapies, it is safe to assume that this and other strategies involving pharmacogenomics will become commonplace.

Hawryluk and colleagues from Foundation Medicine presented data at the 2014 annual meeting of the American Society of Clinical Oncology, which revealed that of 326 pediatric patients with cancer, 241 patients were found to have at least 1 mutation that could be targeted with existing or investigational drugs.[5] When we consider that many of these patients may not have had other US Food and Drug Administration–approved drugs available for their disease states, this type of approach to patients may increase access to high-quality cancer care. Given the paradigm shift that is gradually occurring toward targeted therapies, it is safe to assume that this and other strategies involving pharmacogenomics will become commonplace.

These are but 2 of the trends that have experienced tremendous growth in the recent past. Although we could continue to discuss the role of clinical trials in evaluating novel combination therapies or the trickle-down effect of adult drugs being studied in pediatric populations, it is more interesting for me to consider the recent interest in understanding the molecular mechanisms of pediatric cancers and responding with appropriate drug therapy. This is a service that the pharmacist can provide to the oncology team and one that should not be overlooked as an opportunity to improve multidisciplinary cancer care delivery. ■

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Conquering Cancer Everywhere: A Physician's Perspective

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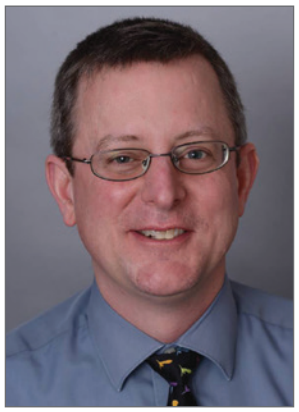
Cure rates for children with cancer now exceed 80% in high-income countries (HIC), but several challenges remain.[1] Curing the remaining 20% requires new drugs, better combination regimens, and improved risk stratification to avoid undertreatment, and the 80% who are event-free survivors after frontline therapy often must deal with significant late toxicities of treatment. Unfortunately, cure rates in low- and middle-income countries (LMIC) fall far short of the 80% achieved in HIC.[2] Addressing the first 2 challenges is a central focus of academic centers and clinical research groups in HIC, but achieving high cure rates in LMIC requires the combined efforts of academia, professional societies, nongovernmental organizations (NGOs), government, and industry. The potential rewards of such efforts for children with cancer worldwide cannot be overestimated, since 90% of children with cancer live in LMIC and can be treated in a local setting at very low cost.[3] Furthermore, lessons learned in LMIC often have implications for children with cancer everywhere, including HIC, and because some clinical trials require large numbers of patients, their feasibility depends on inclusion of children in LMIC.



Scott Howard, MD, MSc

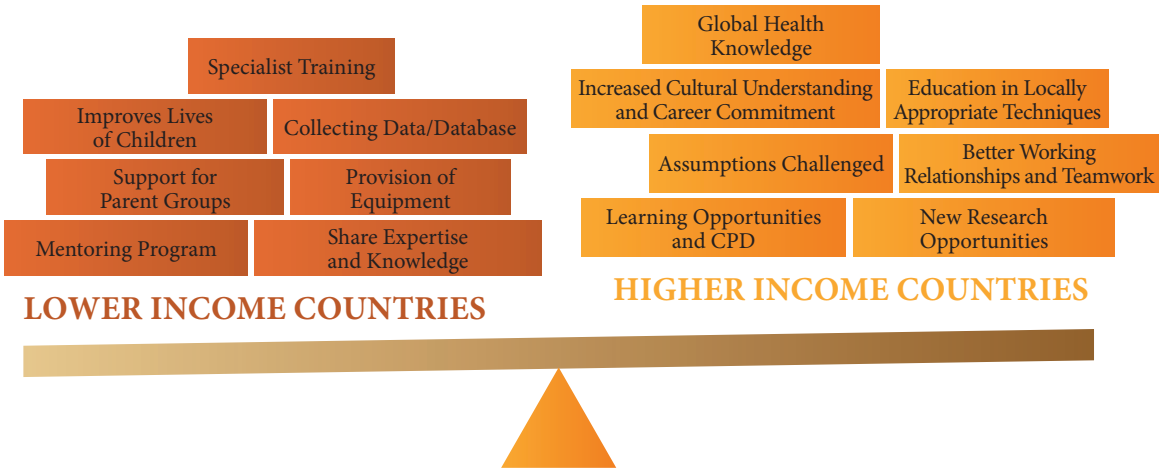
Several strategies have proven effective for curing more children with cancer in LMIC. Three essential strategies are discussed here: (1) addressing preventable causes of treatment failure, (2) adapting treatment regimens to local conditions, and (3) international collaboration via "twinning programs," defined as long-term relationships between institutions to exchange knowledge and improve care for patients on both sides of the relationship.

Implementing programs to address preventable causes of treatment failure, which include treatment abandonment (ie, failure to start or complete medically indicated curative therapy) and excess toxicity-related death, has been shown to increase survival for acute lymphoblastic leukemia by ≥30%.[2,4-7] For example, the Instituto Materno Infantil of Recife, in the relatively poor northeast region of Brazil, reduced the rate of treatment abandonment from 16% to less than 1% by providing subsidized transportation, free oncology care, free housing and food for patients from out of town, and an intensive education and follow-up program.[2] Similar programs have subsequently been deployed in many LMIC centers, where they are extremely cost-effective, since helping a child complete all treatment greatly increases the odds of event-free survival and reduces the need for salvage therapy after relapse, which is associated with increased morbidity and cost.

Adapting treatment regimens for use in LMIC is necessary because cancer centers in these countries often lack certain diagnostic capabilities, risk-stratification tools, chemotherapeutic agents, and, in some cases, radiation therapy. Nevertheless, many children can be cured even in cancer centers with a basic infrastructure, and curing the curable allows such centers to build on their success as resources become available. The International Society of Paediatric Oncology (SIOP, for the initials in French) has a very active Committee on Developing Countries (PODC Committee) that includes working groups focused on adapting treatment regimens, preventing treatment abandonment, improving nursing, facilitating access to essential medications, providing education and training, and ad-

Similar programs have subsequently been deployed in many LMIC centers, where they are extremely cost-effective...

Figure. Twinning programs involve contributions from cancer units in lower income and higher income countries that improve care in both settings.



CPD indicates continuing professional development.
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dressing many other areas necessary to improve cancer care in LMIC. The SIOP-PODC Committee's working group for adapted treatment regimens comprises healthcare providers from all continents, including disease experts, global health experts, and people practicing in both LMIC and HIC. To date, the working group has developed, published, and deployed adapted regimens for 8 common childhood cancers, and others are in the pipeline. Even more important, the working group provides a forum in which to optimize the implementation and further refinement of each regimen to cure the maximum number of children possible in every setting. Regular online meetings are held via www.Cure4Kids.org, developed and supported by St. Jude Children's Research Hospital (St. Jude) to provide educational materials and online conferencing at no cost to users. Besides SIOP, other professional societies, such as the American Society of Hematology and The American Society of Pediatric Hematology/Oncology, also have programs to promote education, training, infrastructure development, and clinical research in LMIC.

Nevertheless, a great deal remains to be done, since, at present, approximately 950 cancer centers in LMIC lack twinning partnerships.

In addition to activities under the auspices of professional societies, international collaboration includes twinning programs between academic centers in HIC and LMIC (**Figure**). For example, St. Jude has 21 such partnerships with centers in Latin America, Africa, Asia, and the Middle East; Texas Children's Hospital supports several programs in Africa; and Boston Children's Hospital collaborates with centers in Latin America, Asia, and Africa.[6,8,9] A number of factors have proven critical to the success of twinning programs (see the essential "C"s in the **Table**), such that, in addition to support from professional societies and academic centers, support from NGOs, government, and industry is also needed and obtained. For example, World Child Cancer (www.WorldChildCancer.org) and Cure2Children (www.Cure2Children.org) are 2 NGOs specifically dedicated to improving care for children with cancer and blood disorders in LMIC, and between them they have funded and implemented twinning projects on all continents except Antarctica.[10-12] Nevertheless, a great deal remains to be done, since, at present, approximately 950 cancer centers in LMIC lack twinning partnerships.

In summary, cure rates for children with cancer in HIC continue to rise, and reducing the late toxicities

Table. Essential "C"s of Successful Pediatric Hematology/Oncology Twinning Programs

Essential element	Components	Description
Commitment by HIC partner	1. Individual leader in HIC (willing to devote time and effort to the program) 2. Institutional commitment to collaborate with a signed memorandum of understanding	1. Defines, develops, initiates, and implements the program 2. Facilitates intra- and interinstitutional communication 3. Engages the hospital and community and mobilizes resources (human, technical, and financial)
Commitment by LMIC partner	1. Individual leader in LMIC (willing to devote time and effort to the program) 2. Institutional commitment to collaborate with a signed memorandum of understanding	1. Defines, develops, initiates, and implements the program 2. Facilitates intra- and interinstitutional communication 3. Engages the hospital and community and mobilizes resources (human, technical, and financial)
Community	1. Nonprofit foundation dedicated to supporting the care of children with cancer 2. One foundation per geographic area 3. The foundation should support children with cancer at all sites within the area, even if treated at a different cancer unit	1. Members of the supporting foundation should include influential members of society, professionals, and parents 2. The foundation must work with both government and the medical team to effect lasting change
Collaborative spirit	1. Respect 2. Trust 3. Humility 4. Collegiality and ideally friendship	1. Relationship of equals 2. Mutual respect 3. Willing to learn from each other 4. Beneficial and enjoyable for both parties
Communication	1. Effective 2. Comprehensive 3. Multimodal	1. Rapid, honest, shared language 2. Addressing programmatic aspects (contracts, money, documentation of activities), patient care (individual cases, protocols, supportive care), continuing education, and hospital infrastructure 3. E-mail, online meetings, phone, bidirectional visits of key personnel
Content	1. Variable 2. According to the needs identified in the LMIC center and the capacity of the HIC center 3. Data collection and outcome evaluation must always be included as a component of the program	1. Goals and specific activities must be very well-defined in writing 2. Goals may change over time by mutual agreement, and should be reviewed at least annually to make sure the most important priorities are being addressed 3. Documentation of causes of treatment failure and death is essential to target interventions and to measure progress
Cash (Funding)	1. The HIC should seek funding to initiate and maintain the twinning relationship 2. Increasing local fund-raising capacity should be part of most twinning programs	Investment of $50,000 per year can have significant impact
Continuity	A long-term relationship is absolutely essential to developing a self-sustaining program	At least a 5-year plan should be developed at the very beginning so that both partners can agree on the goals of the twinning relationship and timing of the included activities

HIC indicates high-income countries; LMIC, low- and middle-income countries.
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of treatment is the subject of very active research. Although extending these cures to LMIC is complex, requiring collaboration of many stakeholders in HIC and LMIC, twinning programs have already improved the lives of countless children with cancer and have laid the foundation to help even more in the future. ■

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