Editorial

Little patients, losing patience: pediatric cancer drug development

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The December 2004 Food and Drug Administration (FDA) approval of clofarabine (Clolar, Genzyme) for refractory pediatric acute lymphoblastic leukemia was a milestone in the history of pediatric cancer drug development. A rare occurrence, it represented approval of a new cancer drug for a pediatric cancer indication without prior approval for an adult cancer indication. This is a major exception, as approval of new cancer drugs for pediatric patients is typically an afterthought to their development and approval for treating adult cancers. In fact, of the 120 new cancer therapies for adults approved by the FDA between 1948 and January 2003, only 30 have shown use in children. Of those 30 drugs, only 15 acquired any labeling for pediatric use during that same 55-year period (1, 2). This disparity in the number of oncology drugs labeled for use in adults versus children is a manifestation of the many challenges faced in pediatric cancer drug development.

So, why has pediatric drug development been the poor stepchild of cancer drug development? What are the major challenges currently confronting pediatric cancer drug development? What are pediatric oncologists and other children's advocates doing to overcome these barriers? Despite these challenges, how have pediatric oncologists managed to make extraordinary strides in improving outcomes for children with cancer?

The Challenges

In general, the major obstacles faced by pediatric oncologists arise from the same underlying issues faced by adult oncologists but are significantly amplified in pediatrics-limited funds, limited time, limited numbers of investigators, limited numbers of patients, and limited political clout. How these factors intermesh to constrain new pediatric cancer drug development is outlined below.

Cancer in Kids Is Not Profitable

Cancer is the most common cause of nonviolent death for children in the United States. One in 300 children will be diagnosed with cancer by the age of 20 years. Yet, the total number of new pediatric cancer diagnoses is miniscule compared with the total number of new adult cancer diagnoses. Whereas 12,000 to 13,000 new cases of pediatric cancer are diagnosed in the United States yearly, a staggering 1,368,030 adults were diagnosed with cancer in the United States in 2004. For additional perspective, there are more cases of breast cancer diagnosed in New York State each year (15,190 in 2004) than there are new pediatric cancer diagnoses nationwide (3). Once pediatric cancers are broken down by individual diagnoses, their numbers relative to adult cancers become exceedingly small.

With the average cost of research and development to bring one drug to market at $802 million and given that 1 in 1,000 new compounds that enter preclinical testing ever make it to human testing and only 1 in 5 agents that enter human trials receive FDA approval (4, 5), it is little wonder that pharmaceutical companies would hesitate to invest in pediatric cancer treatments. Basic economics clearly favors investment in a treatment for 215, 990 adults yearly diagnosed with breast cancer over a treatment for a mere 425 children yearly diagnosed with rhabdomyosarcoma (3, 6).

What can be done to encourage the pharmaceutical industry to develop new drugs for children? In the 1990s, there were multiple unsuccessful attempts to encourage voluntary pediatric studies. In 1998, the FDA finalized the Pediatric Rule, requiring pharmaceutical companies to conduct pediatric studies under certain circumstances. The first studies were required to be submitted in December 2000. However, that same month, the Association of American Physicians and Surgeons, the Competitive Enterprise Institute, and Consumer Alert filed a lawsuit against the Pediatric Rule, claiming that the FDA had no legal authority to mandate pediatric studies. In October 2002, a Federal District Court invalidated the Pediatric Rule (1, 7, 8).

As neither attempts to mandate pediatric studies nor appeals to altruism have proven successful, the FDA has shifted its strategy toward offering financial incentives for evaluating new agents in children. The result is the Pediatric Exclusivity Provision, initially a component of the FDA Modernization Act of 1997 and later renewed from

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January 2002 to 2007 as part of the Best Pharmaceuticals for Children Act. This provision extends patent protection on a new agent for an additional 6 months for pharmaceutical companies that do pediatric studies requested by the FDA. As of February 28, 2006, 117 drugs have been granted exclusivity, of which 10 are oncology drugs (9). Although the Pediatric Exclusivity Provision seems to be having a positive effect, there is no guarantee that it will be extended beyond January 1, 2007 (1, 7, 8).

Kids Do Not Vote

A substantial segment of the U.S. population is disenfranchised because of their age. Simply stated, kids cannot vote. Without a voting block to get the attention of Washington, children must rely on others to make their case for them come budget time. Historically, pediatric cancer has not been a budget priority. For example, the total budget for National Cancer Institute (NCI) for fiscal year 2004 was >$4.7 billion (10). Of that, only $166 million (3 percent) was devoted to pediatric cancers in any form, including funding for prevention, treatment, and long-term follow-up (11).

From a budgetary perspective, it seems that things will only get worse for children with cancer before they get better. For fiscal year 2006, the total NCI budget from the federal government was cut (again) by $39.7 million. This is a major setback for the Children's Oncology Group (COG), the nation's premier pediatric cancer clinical trial organization and a major player in the pediatric oncology drug development world, whose NCI funding has been cut by 10% as a result (Gregory H. Reaman, COG Spring Group Meeting, March 23, 2006).

These cuts translate into fewer clinical trials and scientific inquiries for children with cancer at a time when clinical trial enrollment and resulting access to novel drugs have never been more critical. In addition to short-term issues of survival, increased capital is likewise essential to address the long-term effects faced by childhood cancer survivors from today's toxic treatments (12, 13). As these children now live into their thirties, forties, and beyond, chronic illness and disability are emerging as major challenges. Increased funding is needed both to develop less toxic treatment regimens to minimize late effects and to address those effects when they do occur.

Despite worsening budget constraints, there is a glimmer of hope. One encouraging new development is the Conquer Childhood Cancer Act of 2006. Introduced in March 2006 to the Senate and House of Representatives jointly by Senators Norm Coleman (R-MN) and Jack Reed (D-RI), Congresswoman Deborah Pryce (R-OH), and Congressman Michael McCaul (R-TX), the Act would authorize $100 million for over 5 years to support translational research into pediatric cancers (14). It is too soon to tell whether this bill will successfully pass and whether it heralds a change in priority by our government toward curing pediatric cancer.

Kids' Cancers Are Different

Children and adults are affected by different types of cancers. Even the cancers that are ''common'' to both groups are frequently different on both phenotypic and molecular levels. Molecular profiling of both adult and pediatric cancers will be crucial to understanding these differences as well as uncovering possible overlapping characteristics and treatment targets between children and adults. As cancer drug development moves progressively toward this molecular targeting and away from nonspecific toxins, it is quite possible that the overlap between effective treatments for adult and pediatric cancers will decrease. The more divisive and targeted treatments become, the fewer total patients there are in each disease subgroup. Smaller numbers not only mean less financial incentive to develop new drugs but pose additional challenges as discussed below.

Kids' Cancers Behave Differently

Cancers in adults and children often act and respond differently. For instance, pediatric cancers are frequently more aggressive and rapidly progressive (which sometimes is an advantage for treatment efficacy) than many of the more indolent adult cancers. This is one of the many reasons it is difficult to accrue pediatric leukemia patients onto single-agent phase I trials. Relapsed acute leukemias often progress too quickly for patients to enroll on study and await response. A recent illustration comes from an adult phase III trial in myelodysplastic syndrome, which showed that the median response time to decitabine, a demethylating agent, was 3.3 months. This is far too long to wait for a rapidly progressive pediatric acute leukemia (15). Pediatric oncologists have tried to address this issue by using newer clinical trial designs, such as administering novel agents in brief windows followed immediately by administration of combination cytotoxic chemotherapy. They have also moved toward eliminating single-agent phase I leukemia trials altogether, choosing instead to extrapolate toxicity and dosing information from pediatric solid tumor and adult leukemia trials.

Too Few Kids

Besides the financial disincentives to developing new pediatric cancer drugs due to the small patient base, the limited number of pediatric cancer patients presents other challenges. Even with the dearth of pediatric cancer–specific drugs, there are more new oncology drugs in development with potential activity in pediatric cancers than there are pediatric patients in whom to evaluate them. How do we choose which drugs to evaluate? How do we make decisions using limited numbers of patients? How can we complete studies more efficiently? Because of small patient numbers, clinical researchers in pediatrics are often forced to weigh the consequences of conclusions drawn from studies with limited statistical power. By using fewer patients, the increased risk of both type I and type II errors may result in moving forward ineffective drugs or discarding effective ones. Novel approaches to clinical trial design are needed, including designs that require fewer patients. Some adult cancer drug studies have already begun implementing new trial designs. These need to move quickly into the pediatric realm, where the need, based on limited patient numbers, is far greater.

For phase I trials, one approach is to determine dosing based on molecular response in lieu of continuing to enroll patients at escalating doses until a maximum tolerated dose (MTD) is reached. However, which molecular end points have clinical significance? Which end points truly correlate with the anticancer mechanism of the drug? How do we determine statistical significance or draw a ''positive/negative'' line on a biological continuum? These are just a few of the many questions that require creative answers if we are to move our clinical trial design into the 21st century to match the current age of drug development.

Kids Get the Hand-Me-Downs

As discussed previously, it is rare that a drug is brought to evaluation in children before completion of at least one adult trial. Phase I pediatric trials are initiated an average of >2 years after the adult phase I trials are published (2). This traditional pattern of evaluation, which effectively relegates children to second-class status, further delays newer treatments from reaching children.

Kids Are Not Little Adults

Pharmacokinetics, efficacy, and toxicity can be different between children and adults, which limits the utility of extrapolating data from adult trials.

Limited Preclinical Models for Kids' Cancers

There are limited preclinical models available for pediatric malignancies. Traditionally, pediatric tumors have not been included in the NCI panel of cell types used to screen potential anticancer compounds. The Cancer Therapy Evaluation Program of the NCI recently addressed this gap by initiating a Pediatric Preclinical Testing Program, which makes use of cell lines and animal models for pediatric tumors to test new compounds (2). The program is currently evaluating 11 to 12 new agents yearly (Malcolm A. Smith, COG Spring Group Meeting, March 23, 2006). These pediatric-specific preclinical models enable more efficient evaluation of new drugs and prioritization of which drugs to move forward to pediatric trials. Additionally, this program includes testing of pediatric tumor tissues and cell lines for gene and protein expression, thus facilitating the development of molecularly targeted drugs for pediatric tumors (2).

Too Few Formulations for Kids

The average age a child can begin swallowing pills is 7 years. For younger children, inability to swallow oral agents poses a significant treatment obstacle. If an oral agent has no liquid formulation and the pill form cannot be crushed, patients may have no other treatment options available. There is currently little financial incentive for pharmaceutical companies to invest the time, effort, and capital needed to develop pediatric liquid formulations. Consequently, a pediatric oncologist may be left to tell parents that no treatment is available for their 5-year-old child because he cannot swallow a pill.

Ethical Considerations with Kids

Institutional Review Boards are much more cautious when it comes to ''experimenting'' on children. A parent's ability to ''consent'' on behalf of a child may be more limited than that parent's ability to consent to treatment for himself or herself. For instance, in an effort to evaluate a molecularly targeted drug, it would be ideal to obtain a sample of tumor tissue after a drug is administered to evaluate for effect on the desired target (this is often done in the adult oncology world). But, is it ethically appropriate to subject a child on a phase I study to the pain involved with a repeat tumor biopsy to assess molecular response? Can we ethically ask a parent to consent to that? These ethical considerations often lead to use of surrogates, such as normal peripheral blood mononuclear cells, to evaluate target modulation. Effects on these surrogates, however, may not accurately reflect the activity of the drug in the malignant cell.

Another controversial issue plaguing Institutional Review Boards nationwide is whether a child can or should consent on his or her own behalf to participate in a study (called ''assent''). Questions abound. At what age, if any, is assent appropriate? Is true informed ''assent'' even realistic? How should differences in children's developmental levels be taken into account? Should the type of study (e.g., phase III for a newly diagnosed patient versus phase I for a relapsed patient) affect how much say a child has in the decision to participate? To address these and other issues, the COG Bioethics Committee convened a multidisciplinary task force in 2003 to address issues of assent and to formulate guidelines for pediatric oncology (16).

The Successes

Despite all of the challenges in developing new pediatric cancer drugs, outcomes for children with cancer have improved steadily to a current overall event-free survival of ~75% (17). Clearly, pediatric oncologists have confronted daunting obstacles yet have somehow managed to work around them, often outpacing their adult oncology counterparts. The many successes in pediatric oncology can be attributed to a variety of factors.

Kids' Well-Oiled Clinical Trial Machines

Pediatric oncologists have integrated clinical trials into a culture of standard practice. Whereas only 2% of adult cancer patients enroll in NCI-sponsored clinical trials, 50% of children with cancer do (18). COG is a well-established, well-organized clinical trial machine. As with any large organization, efficiency could be improved, but the overall success of COG and its predecessor organizations has been extraordinary. Other complementary pediatric cooperative groups have also emerged, enabling even more drugs to be tested and giving patients greater access to new agents.

Kids Have Parents

Medical staff and families are especially aggressive about seeking cures for children with cancer. Consequently, parents, with the support of an enthusiastic and encouraging medical staff, are highly motivated to enroll their children on clinical trials.

Response Assessment Easier in Kids

As noted previously, pediatric tumors are often more rapidly progressive than many of the more indolent tumors found in adults (e.g., sarcomas versus carcinomas). This is

one reason pediatric cancers are frequently more responsive to cytotoxic therapy, which targets rapidly dividing cells. This in turn impacts the approach to clinical trial design. Rapid response allows efficacy assessments to be carried out sooner, supporting the use of early response as a surrogate marker and thereby expediting drug development.

Kids Are (Otherwise) Healthy

Children typically have good underlying organ function. They can usually tolerate more aggressive, more toxic treatment.

Kids Make Hand-Me-Down Fit

Although the progress of pediatric drug development is delayed while awaiting initial adult clinical trial results, this carries some advantages. By the time pediatricians are conducting a phase I trial, adult data on toxicity is available. Dose escalation can then be based on the adult MTD. Because children tolerate toxicity better than adults, the pediatric MTD is rarely less than the adult MTD. Typically, the initial dose level in a pediatric phase I will be 80% of the adult MTD and the dose will escalate from there. This helps limit both the total number of patients needed to complete a pediatric phase I trial as well as the number of patients treated at lower, often subtherapeutic doses. Additionally, adult trials provide preliminary efficacy data. This can help in prioritizing which drugs to bring into pediatric trials. While care must be taken when extrapolating efficacy data from adult studies to pediatrics, doing so can provide useful information beyond preclinical models.

The Future

Despite our success in markedly increasing survival in pediatric cancer patients, there is much work to do. We need better science to unravel the molecular underpinnings that drive childhood cancer. We need better agents for children who do not respond to currently available treatments. We need better clinical trial designs to increase efficiency of the drug development process and to optimize how we treat children with the new generation of anticancer drugs. We need better approaches to the short- and long-term toxicities of treatments, from major organ toxicities to secondary malignancies, which will hopefully decrease with the rational use of molecularly targeted agents.

Although many obstacles remain for pediatric cancer drug development, none are insurmountable. No longer able to wait patiently, our little patients require the ingenuity, creativity, cooperation, and perseverance of individuals and organizations dedicated to putting themselves out of business.

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