Development of Molecularly Targeted Therapies to Treat Pediatric Malignancies

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Drugs and biologics developed to treat children with cancer have been historically developed in adults for adult indications. Although leading to many useful drugs and biologics to treat pediatric cancer, future development of molecularly targeted therapies (MTTs) should be directed toward pediatric tumors more specifically to maximize antitumor efficacy while minimizing acute morbidity and long-term disability. This will put pediatric clinicians closer to the goal of cure for all children diagnosed with cancer.

According to the latest statistics, cancer is the leading disease-related cause of death in children 1–14 years in the United States. In 2017, 10,270 children from birth to 14 years will be diagnosed with cancer and almost 1,200 will die from this diagnosis. Progress has been made in treating children with cancer, as evidenced by conversion of pediatric acute lymphoblastic leukemia from an incurable disease in the 1950s to one in which over 90% are cured of their disease.[1] Yet, for some cancers, the progress has been very limited (e.g., diffuse intrinsic brainstem gliomas), and for those patients surviving their therapy long-term morbidity is often associated with the therapy affecting their quality of life. Thus, the challenge for those discovering and developing new therapies for childhood cancer is to find specific molecularly targeted therapies (MTTs) that optimize antitumor efficacy while minimizing damage to normal tissues, which results in acute morbidity and long-term disability.

Not unlike conventional chemotherapeutic drugs routinely used to treat children with cancer, MTTs are typically first developed in adult clinical trials. This approach has led to the introduction of many useful drugs and biologics to the therapeutic armamentarium of the pediatric oncologist and has several theoretical advantages. A *priori* one might presume overlap of fundamental cell signaling pathways that are disrupted during development of pediatric and adult cancer.[1] Many of the altered molecular pathways observed in adult cancer have been extensively studied in the laboratory and clinic, providing the pediatric investigator an information advantage as they begin their studies in their pediatric model. Last, the fact that drugs or biologics are developed for the altered molecular pathways in adult tumors makes them available for testing in pediatric malignancies. An example of this is the BCR-ABL translocation, present in both adult chronic myelogenous leukemia and pediatric acute lymphoblastic leukemia, leading to the successful use of imatinib to improve event-free survival in both diseases.

As MTTs are developed for pediatric tumors, it is critical that molecular targets in the pediatric tumor of interest be carefully defined. As noted earlier, drugs and biologics developed first in adults have been subsequently used in children with cancer and found to provide clinical benefit. Still, studies should be performed to confirm that the molecular target or pathway is active, functions, and plays a role in maintaining the pediatric cancer prior to trialing an agent in the disease of interest. Often, pediatric patients will receive a drug that has been successfully tested in adults without convincing rationale that it may work in the pediatric disease. This leads one to question the connection between an adult tumor with a particular molecular target lesion and the pediatric tumor of interest.

The fundamental basis for the application of precision medicine, as defined in the National Academy of Sciences 2011 report,[2] is the ". . .ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment." In actuality, pediatric oncology has been on the forefront of applied molecular characteristics and precision medicine. Current pediatric clinical trials are heavily molecularly informed and subgrouping pediatric tumors based upon molecular characteristics is commonplace (e.g., MYCN for neuroblastoma and FLT3-ITD for acute myelogenous leukemia). Moreover, recent medulloblastoma protocols divide patients into different molecular subgroups and risk-stratify accordingly.

However, absent from the vast majority of these protocols are specialized medications targeting the identified molecular differences. Although the low-risk identification serves to dose-reduce highly toxic regimens for patients predicted to do well, very little change is implemented for patients with high-risk refractory disease. Two major reasons for lack of targeted medications in these patients are access to available drugs and availability of unique drugs active in the pediatric disease.

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Received 17 May 2017; accepted 29 June 2017; advance online publication 24 August 2017. doi:10.1002/cpt.785

At face value, pediatric patients with cancer seem much better candidates for MTTs than adults. Pediatric patients tend to have fewer underlying morbidities and, thus, are healthier than adults. Pediatric cancers also have lower rates of mutation across their genomes when compared against adult cancers. Fewer mutations per tumor suggests fewer altered cellular pathways and, therefore, potentially more activity in a pediatric tumor (i.e., more specificity).

Despite this reasoning, MTTs in children remain an afterthought. The rarity of pediatric cancer means that pharmaceutical companies are unlikely to market their novel drugs in such a small population, and the vulnerable status assigned to children means that pharmaceutical companies are reticent to experiment in patients who cannot consent for themselves. To an extent, this means that pediatric oncology will continue to remain reliant on drugs manufactured for adult indications, but, thankfully, all is not lost by an approach that prioritizes adult disease. Fundamentally biologic systems are widely conserved and the redundancy of cellular growth pathways means a finite number of targets and/or pathways can be targeted. Molecular and sequencing data support this and demonstrate molecular overlap between adult and pediatric disease. For example, deregulation of CDK, MAPK, and PI3K pathways are as common in pediatric cancers as they are in adult malignancies. Additionally, targetable activated oncogenes seen in adult tumors have been identified in pediatric tumors. For example, BRAF V600E is widespread in adult melanoma and present in both pediatric low and high-grade gliomas.

Although the relevance of some adult targets has been confirmed, many molecular aberrations identified in pediatric tumors have not been matched with currently marketed drugs. This results in a tendency to pursue a drug's downstream or off-target effects when it probably only has minimal activity in this area. This is illustrated by the use of dasatinib as a platelet-derived growth factor receptor inhibitor against brain tumors instead of BCR-ABL inhibitors. Similarly, histone deacetylase inhibitors are being proposed as targeted therapy for mutations (e.g., H3K27M) that confer a methylation rather than acetylation defect. EZH2 inhibitors, designed to target activating mutations in EZH2, seen mainly in lymphoma, are being trialed in rhabdoid tumors with SMARCB1 mutations due to a potential reliance of EZH2 enzyme for proliferation.[3] This strategy is not completely flawed and often supported by preclinical data, but the expectation that a single agent designed for one purpose may have significant activity on another downstream or off-target abnormality may be unrealistic. When taking this approach, dose, schedule, and potentiating combination partners should be reconsidered. Trials taking these factors into consideration should be designed and supported around this novel idea and not simply mimic previous adult strategies that were designed for a different purpose.

Finally, it may be that certain molecular aberrations will be solely confined to pediatric tumors. RELA fusions in ependymoma or H3K27M mutations in diffuse intrinsic brainstem gliomas may not have adult counterparts by which to stimulate drug development.[4] Here, the problem of how to identify a therapy continues to loom large and novel strategies to support and promote targeted therapy for these diseases should be realized.

Regardless of whether overlap is observed between adult and pediatric targets or not, access for pediatric patients with cancer to MTTs is sorely lacking. For example, for drugs with targets in common between adults and children, it may be common for thousands of adult patients with cancer to have received the agent before the first child is enrolled on a clinical trial. This time-lag to pediatric access and the massive imbalance of treated adults to treated children must be addressed. However, to bring these novel strategies to children will require the continued effort of the US Food and Drug Administration and European Medicines Agency as well as public/private partnerships. In 2005, the Institute of Medicine released a report calling for these partnerships to lead the discovery and development of pediatric cancer drugs so that children can benefit from the new wave of science and molecularly targeted medicine for cancer. Public policy changes are also neccessary, such as HR 1231 Research to Accelerate Cures and Equity for Children Act, which is an update to the Pediatric Research Equity Act allowing the US Food and Drug Administration to require studies based on molecular markers rather than indication. Also, use of novel clinical trial designs, such as those proposed by the Innovative Therapies for Children with Cancer Consortium, will enable the study of new agents to use fewer patients, identify active agents quicker, and ultimately move those agents into the clinic to treat children and adolescents with cancer.[5]

SUMMARY

As pediatric cancer is rare, it is difficult for pharmaceutical companies to justify development of therapies directed specifically toward pediatric oncology indications purely from a market perspective. However, to continue to reduce the leading cause of disease-related death in children, we must optimally develop drugs that come from adult indications and identify ways to find unique drugs to treat molecular aberrations identified in pediatric tumors. This way we can achieve our long-term goal of a cure for every child diagnosed with cancer.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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