INTERNATIONAL SOCIETY
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New Drug Development for Children with Cancer

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Abstract

Since the introduction of chemotherapy more than 50 years ago, the prognosis of childhood cancer has improved dramatically, with overall 5-year survival rates approaching 80%. Despite these advances, several childhood cancers still have unacceptably low cure rates, and even when treatment is successful, the acute and long-term morbidity of current therapy can be substantial. Over the past decade, progress in our ability to improve the outcome for children with cancer has slowed significantly. We are, however, entering an era with the potential to understand the molecular basis of all childhood cancers in a timeframe previously unimaginable. At a national level, however, our cancer clinical trials infrastructure faces a number of challenges, most notably the ability to move new ideas forward towards successful clinical trials in a timely manner. Our clinical trial resources will need to be primarily focused on diseases with poor to moderate outcome where there is a clear rationale to investigate a relevant targeted new agent. Coupled to this challenge will be to design trials that can clearly isolate the effect of a new agent under study. The most significant near term change may well be in the design of phase II trials, with incorporation of randomized designs needing to be increasingly utilized. Academic centers, government, industry and patient advocates must work together towards a common goal of leveraging discoveries into improved outcomes for all children with cancer.

Since the introduction of chemotherapy for the treatment of childhood leukemia more than 50 years ago, (1) the prognosis of childhood cancer has improved dramatically. The 5-year survival rate for childhood cancers, many of which were uniformly fatal in the pre-chemotherapy era, was 80% for all forms of childhood cancer diagnosed between 1996 and 2004. (2) This improvement in survival is a result of the incorporation of anticancer drugs into treatment regimens that previously relied only on surgery or radiotherapy for the primary tumor. The multimodality approach, which integrates surgery and radiotherapy to control local disease with chemotherapy to eradicate systemic disease, has become the standard approach to treating most childhood cancers.

Despite these advances, several childhood cancers still have unacceptably low cure rates, (3) and even when treatment is successful, the acute and long-term morbidity of current therapy can be substantial. (4,5) As detailed in recent report based on data from the Surveillance, Epidemiology and End Results (SEER) Program, over the past decade progress in our ability to improve the outcome, as measured by the overall mortality rate, has slowed substantially for children with cancer, most notably for children with solid tumors. (6)

Over the past 35+ years, the overarching strategic approach for most childhood cancer treatment, intensification of therapy, is no longer yielding meaningful improvement in survival. As is well known to pediatric oncologists, children who receive standard dose-intensive chemotherapy have greater than an 80% chance of having at least one drug-related toxicity that is severe, life threatening or fatal over the course of their treatment, (7) and the late effects of cancer treatment, including permanent organ and tissue damage, hormonal and reproductive dysfunction and second cancers, are of special concern. Perhaps more startling is a recent report that, relative to the general population, the overall life expectancy for survivors of childhood cancer is shortened by 10 years. (8) Thus the development of new anticancer drugs must be a priority for childhood cancer basic, translational and clinical researchers.

We are entering an era of an unprecedented pace of discovery in cancer research. Costs associated with whole genome sequencing and related methods are falling precipitously, and thus our ability to understand the molecular basis of all childhood cancers is potentially within reach in a timeframe unimaginable just five years ago.

It is likely that a number of molecular targets will be defined for which there are therapeutic approaches currently available or in clinical development for adult cancers. The key question will shift from the laboratory back to the bedside as we ask how we will leverage this knowledge into an improved outcome for children with cancer.

At a national level, our cancer clinical trials infrastructure faces a number of challenges. A recent report from the Institute of Medicine (IOM), "A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program," details the current problems and suggests pathways forward (9). The one pediatric group funded by the National Cancer Institute (NCI), the Children's Oncology Group, does not share all the challenges facing the nine adult cancer cooperative groups. Yet an overarching theme of the report, the ability to move new ideas forward towards successful clinical trials in a timely manner, is indeed a common challenge. Thus if we are to capitalize on the era of discovery, we must fully re-evaluate how we develop novel therapeutic approaches for children with cancer, and in doing so, re-invent the approach to our cancer clinical trials system.

Over the past decade, the most active area of cancer drug development has been in agents that target signaling pathways, most notably tyrosine kinase (TK) pathways. Tyrosine kinases are a family of enzymes that are responsible for transferring phosphate residues from ATP to the hydroxyl group of tyrosine; the phosphorylation of their intended target can lead to a wide array of actions, including cell division, migration, and upregulation of cellular metabolism. (10) The majority of TKs are transmembrane glycoproteins that dimerize upon ligand binding (receptor tyrosine kinase, RTK); others are cytosolic or nuclear non-receptor TKs that are triggered downstream by RTKs. (11) The vital function of TKs makes them ideal targets for

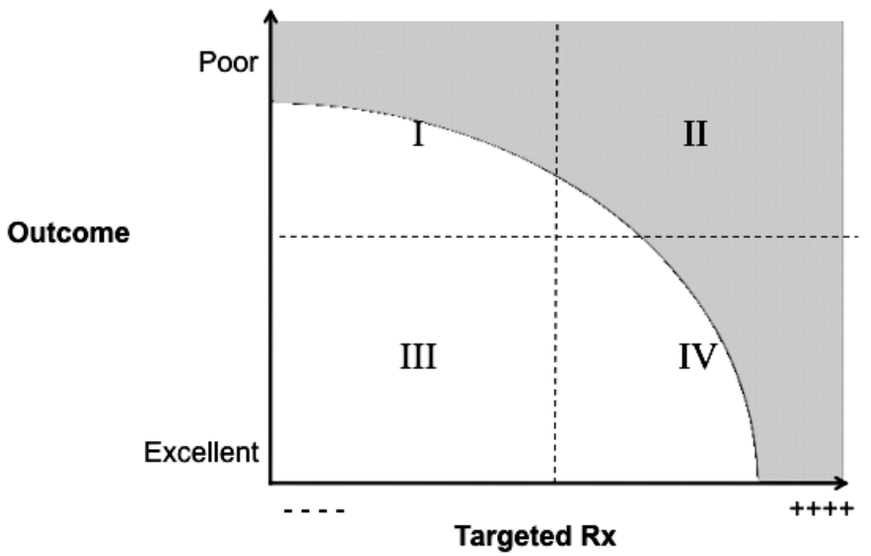

Figure 1.

A re-alignment of clinical trial resources will need to occur if we want to better leverage discovery into improved outcome. Over the past 15 years significant resources have been focused in quadrant III: diseases for which the outcome is relatively good but the ability or availability of targeted new agents is limited to non-existent. We must shift resources primarily to quadrant II: diseases for which the outcome is moderate to poor but our ability to deliver a relevant targeted new agent is reasonably high. As we transition resources, there will still be a need to launch clinical investigations for diseases with very poor outcomes despite a limited knowledge of the molecular basis of disease; moreover, strong consideration should be given to diseases with reasonably good outcomes where a highly relevant targeted therapy is developed (shaded areas).

oncogenic mutations, and altered TK function via proto-oncogene transformation, overexpression, translocation, or deletion contributes to the malignant potential in several human cancers. For example, tyrosine kinase inhibitors currently in clinical use which have or are poised to undergo early phase testing in children (12) include agents that target BCR-ABL — imatinib mesylate, nilotinib and dasatinib; agents that target the epidermal growth factor receptor (EGRF) — erlotinib, geftinib and cetuximab; and agents that target vascular endothelial growth factor (VEGF) — bevacizumab, sunitinib and sorafenib. A wide spectrum of other TKIs are in various stages of clinical development, including agents that target the insulin growth factor receptor (IGFR-1), anaplastic lymphoma kinase (ALK), protein kinase B (AKT), and numerous other pathways. The remarkable homology in the kinase domain of both receptor and cytoplasmic tyrosine kinases has indeed provided a pharmacological opportunity that the biopharmaceutical industry has vigorously pursued. Targets beyond enzyme associated signaling pathways, however, have proven more elusive to therapeutic development.

Although our current understanding of the molecular basis for childhood cancers is variable, we can anticipate a rapid increase in this understanding. A primary limitation on therapeutic advance will be availability of agents capable of effectively impacting key targets. Thus, when coupled to our current knowledge of the value of relevant molecular targets, one key set of factors that must be considered in re-aligning our prioritization of clinical trials is the ability, and availability, of targeted new agents. Of equal importance is the current outcome for the cancer sub-populations being considered for clinical investigation. There are clearly a number of childhood tumors that have not benefitted from any meaningful therapeutic advance for many years, and in the absence of a better understanding of their molecular basis, we will likely need to continue rational, but largely empiric, approaches to clinical trials. A high level view of the approach needed is shown in the Figure. Ideally, our resources should be focused on diseases with moderate to poor outcome where our ability to deliver a relevant targeted new agent is high. Conversely, diseases with good to excellent outcomes, with either a limited understanding or ability to administered targeted agents, should not be a near term focus of clinical investigation resources.

Another key challenge will be to design trials that can clearly isolate the effect of the new agent under study. We can no longer afford to conduct large-scale trials that compare regimens that do not afford a clear understanding of the basis for improvement in outcome beyond the comparison of the regimens themselves. Our clinical trial designs must be able to clearly define the effect of therapy that impacts a specific target. Such designs will potentially allow for an extrapolation of results beyond a fixed regimen.

Perhaps the most significant challenge will be in our design of phase II trials. Demonstration of significant single agent clinical activity in a relapsed population will likely continue to be the most reliable mechanism to advance a new agent to further investigation. For many agents, however, there may be a strong inclination to combine the novel agent with more traditional active but non-curative cytotoxic agents. Interpretation of such trials is inherently difficult and fraught with error. Pursuit of randomized phase 2 trials, including trials that compare distinct targeted agents in conjunction with a common cytotoxic chemotherapeutic regimen, will be but one novel design approach that merits pursuit.

Lastly, we must better position programs to foster enhanced collaboration. The ability to develop and execute clinical trials in a timely manner will greatly enhance our ability to partner with biopharmaceutical partners. Our already small disease populations will become smaller as the molecular basis for these cancers dissect the historic pathologic classifications of disease into sub-populations potentially requiring distinct targeted therapies. Thus developing infrastructures that allow for better international collaborative studies is essential. Moreover, exploration of novel designs that can yield interpretable results with smaller populations will be important.

The next 10 years will be both exciting and challenging. Our approach to clinical trials must evolve in concert with the discoveries made in our laboratories. Academic centers, government,

industry and patient advocates must work together towards a common goal of leveraging discoveries into improved outcomes for all children with cancer.

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