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New insights into drug development for pediatric solid tumors: what preclinical data justify clinical trials in pediatric cancer?

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"Development of uniform criteria for preclinical studies that are necessary for supporting clinical investigations would benefit both pharmaceutical companies in preparing pediatric implementation applications, but also bring some uniformity to pediatric drug development in general, that ultimately will benefit pediatric patients."

Childhood cancer is rare, and in the USA approximately 70% of children diagnosed with cancer are cured, with the 5-year event-free survival rate close to 80%. Consequently, there are relatively few opportunities to evaluate experimental agents, and development of new therapies can be a slow process. However, the criteria by which agents are selected for evaluation in Phase I and II clinical trials are not well defined. What preclinical data should be required to justify clinical trials in pediatric cancer patients, and what types of data could be useful in preparing pediatric implementation plan applications for federal agencies, are considered in this article. Development of uniform criteria for preclinical studies that are necessary for supporting clinical investigations would benefit both pharmaceutical companies in preparing pediatric implementation applications, but also bring some uniformity to pediatric drug development in general, that ultimately will benefit pediatric patients.

Pediatric cancer is rare with approximately 12,000 cases per year diagnosed in children and adolescents in the USA. Consequently, development of novel drugs to treat specific pediatric cancers is far from the radar screen for most pharmaceutical companies. Rather, pediatric cancer tends to come into view quite late in the drug development process. As a consequence, the FDA and the EMA have instituted processes to enhance the entry of new agents into pediatric clinical trials. Primary concerns have been to avoid exposing children to unnecessary trials. For example, evaluation of drugs indicated for conditions that do not present in the childhood population (e.g., Parkinson's disease). Regulations are also designed to enhance science and decrease the risk to children during pediatric product development. The Pediatric Implementation Plan (PIP), developed by the EMA, further defines the clinical trials to be conducted in children. While the goals set out by these agencies are laudable, it is unclear what the data requirements are to define which clinical trials are justified. On a broader scope, what preclinical data should be required to justify clinical trials in pediatric cancer patients?

There are clear examples where development in children can rationally follow that in adults. For example, where a common genetic etiology exists as with the reciprocal chromosomal translocation

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in Ewing sarcoma that leads to the EWS1/FLI1 chimeric transcription factor in both adult and childhood disease, mutations in BRAF ($BRAF^{V600E}$) common to many melanomas and some low-grade gliomas in children, BCR-ABL activation as in chronic myelogenous leukemia. Similarly, where a common surface epitope is expressed in adult and childhood cancers for development of antibody–drug conjugates. Unfortunately, these examples are relatively rare. Adults develop mainly epithelial tumors, and adenocarcinoma is exceedingly rare in children. Thus, agents that demonstrate significant activity in adult trials against cancers such as breast, prostate, lung or colon, the major focus for pharmaceutical drug development, may or may not have application for treatment of childhood malignancies.

Thus, apart from those rare instances where the path to pediatric development is clear, how does one proceed with 'rational' drug development in the environment of pediatric cancer? Preclinical models for pediatric cancers exist, both established cell lines that represent many cancer histotypes, as well as patient-derived and cell line-derived xenografts in immune-deficient mice. There are an increasing number of genetically engineered relevant models of pediatric cancers in syngeneic hosts that may be valuable in identifying both conventional agents, but also agents that modulate immune responses. Thus, one can envisage generating preclinical data similar to that used in development of the agent for use against adult malignancies. However, the attrition rate for cancer drugs exceeds 90%, an unenviable track record [1]. The reasons for failure of an agent are numerous [2], although for many agents, clinical failure is related to inability to reach drug exposures that are relevant to target inhibition in patients, or due to adverse toxicities not identified in non-human species. While the anticipated human systemic exposure to an agent can be estimated through allometric scaling approaches, the actual range of exposures in patients treated at the recommended Phase II dose (RP2D) may be critical information in development of such agents for pediatric use, as it could eliminate one of the major reasons for failure in a clinical setting. For example, with pharmacokinetics information it is relatively easy to expose cells *in vitro*, or dose tumor-bearing mice to achieve drug exposures that are relevant to clinical use. This is particularly important if meaningful preclinical data relevant to clinical application are to be obtained [3–5]. Indeed, targeting drug exposure to achieve those in mice that led to regression of neuroblastoma xenograft demonstrated the response rate predicted from the preclinical models [6]. Exposures to drugs at concentrations that dramatically exceed those achievable in patients are of little relevance, and can lead to design of trials that ultimately fail. Similarly, there are numerous examples where human tumors in mice regress upon treatment with agents at dose levels and schedules giving drug exposures that cannot be achieved in patients. The one advantage of 'following' the adult Phase I trials is that such pharmacokinetic data are usually available when conducting preclinical investigations that relate to use of that agent in children. These data can be critical in making decisions as to whether to proceed to pediatric clinical trials with an agent [7,8].

Despite availability of pharmacokinetics data from Phase I trials in adults, this information is factored into relatively few pediatric preclinical studies. Demonstration that tumors respond (i.e., regression, or definitive pharmacodynamics data showing target inhibition) at clinically relevant doses and schedules in mice would seem imperative in generating a comprehensive data set to justify testing in children.

The emphasis for PIPs is largely driven by safety issues, while development of the design for clinical trials is directed toward proving the efficacy of the agent being developed. Whereas preclinical development of novel agents for adults follows 'industry standards,' there is a lack of uniformity in pediatric development where most studies are conducted by academic laboratories. Recent reviews attest to irreproducibility of results from academic laboratories in an industry setting [9,10]. Yet, there are no standardized criteria used in advancing agents toward pediatric clinical trials. It is critical to set uniform standards for preclinical studies that will allow cross-agent comparison, and identify hisotypes where the greatest probability of efficacy will be realized. Such data sets are not only valuable in designing studies for PIP applications, but may focus clinical evaluation on patient populations most likely to benefit, and reduce the recruitment of children to trials where there is a low chance for benefit. These studies also offer the opportunity to demonstrate differences between approved agents and the experimental agent. The challenge is to bring order to the current plethora of approaches used to generate data to justify pediatric clinical trials.

One approach to developing robust data sets that may support pediatric cancer drug development is the pediatric preclinical testing program (PPTP) supported through the National Cancer Institute [101]. This program has developed uniform models for sarcoma (Ewing, rhabdomyosarcoma, osteosarcoma), neuroblastoma, brain tumors (glioblastoma, ependymoma, medulloblastoma and atypical rhabdoid teratoid [ATRT] tumors), kidney tumors (Wilms, ATRT) and acute lymphoblastic leukemias. The childhood tumor xenografts are largely patient derived, and 23 cell lines representing pediatric cancer histotypes are used for *in vitro* screening. Each tumor or cell line has been extensively characterized by expression profiling, single nucleotide polymorphism (SNP) analysis and exome sequencing is currently underway for all models. Importantly, the PPTP has developed standard approaches to agent evaluation, criteria for defining clinically relevant responses and the ability to identify 'omics' signatures with tumor responses [11]. While resources required to evaluate an agent in 45 primary xenograft models and 23 cell lines, can obviously not be duplicated in most academic laboratories, it should be possible in a pharmaceutical company. While the PPTP approach has merit, it also is limited to a relatively few tumor models to represent particular pediatric cancer types. With increasing sub-classification of these rare tumors based upon genomics information, it will be important to have adequate representation of genetic subtypes within any panel. Another limitation is that because tumors are propagated in immune-deficient mice, the models are not

particularly relevant for testing immune-based therapies. For such agents, genetically engineered mice representative of particular pediatric cancers may be optimal.

Based upon the considerations discussed above, can recommendations be made regarding 'standardized' criteria that should be required for supporting clinical trials in pediatric patients that would be beneficial for pharmaceutical companies submitting PIPs or for consideration by disease committees in the Children's Oncology Group (COG), or local IRBs? Most preclinical data are generated using cell lines in culture. Can one move directly from *in vitro* cell culture to the clinic, and if so what data would support this? As discussed above, it is essential that drug exposures are relevant to clinical exposures when conducting these experiments. This is particularly important where the agent is cleared rapidly from plasma. Claims that particular cancer types are hypersensitive to a particular agent should be supported by comparison with sensitivity of panels of tumor cells derived from different pediatric tumors. For example, it was claimed that cytosine arabinoside was selectively toxic to Ewing sarcoma cells, however the comparators were four carcinoma cell lines [12]. By contrast, Ewing sarcoma cells were >20-fold less sensitive than acute lymphoblastic leukemia cells, a disease known to be responsive to this agent [13]. Similarly, evidence for synergy by drug combinations should take into account the clinical pharmacology of each agent, and evaluate potential synergistic toxicity in a relevant model system where available. For *in vivo* studies, specific response criteria should be established. These criteria may differ according to the drug under study. For example, cytostatic or antiangiogenic agents are unlikely to induce tumor regressions, whereas cytotoxic agents (even those molecularly targeted agents that target essential processes such as mitosis) should induce regression in models if regression is to be used to define clinical activity. Thus, development of clinically relevant response criteria is important, for example, 80% tumor growth inhibition represents progressive disease in a clinical setting. Evaluation of efficacy in clinical Phase II trials is based upon outcome for 12 patients, yet we accept data generated from a single animal model to justify moving an agent, or combination of agents, to clinical trials in children. Clearly, resources required to evaluate agents in 12 xenograft models are substantial, but vastly less costly than running clinical trials that fail based upon poor or incompletely developed preclinical data [14]. The PPTP approach has been to evaluate agents against small panels of tumors comprising 6–8 models each representing a different histology, akin to a 'mini-Phase II' evaluation. For truly active agents that subsequently demonstrated clinical utility, there is a robust signal [15,16] where at least 50% of models within a panel have demonstrated regressions [4]. There will be circumstances where fewer models representing a specific genotype are available to evaluate targeted agents, and in those instances data from individual models may be the best we can provide to guide clinical development. However, for most indications a spectrum of pediatric cancer models are available, hence reporting of modest activity in a single model to justify clinical evaluation of a drug or drug class, despite genomics data to validate the target, seems unacceptable [17]. Development of uniform criteria for preclinical studies that are necessary for supporting clinical investigations would benefit both pharmaceutical companies in preparing PIP applications, but also bring some uniformity to pediatric drug development in general, that ultimately will benefit pediatric patients.

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