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Enrolling Adolescents in Disease/Target-Appropriate Adult Oncology Clinical Trials of Investigational Agents

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Abstract

The enrollment of adolescents with cancer in clinical trials is much lower than that of younger pediatric patients. For adolescents with "adult-type" cancers, lack of access to relevant trials is cited as one of the reasons for this discrepancy. Adolescents are generally not eligible for enrollment in adult oncology trials, and initial pediatric trials for many drugs are conducted years later, often after the drug is approved. As a result, accrual of adolescents to these trials may be slow due to off-label use, prospectively collected safety and efficacy data are lacking at the time of initial approval, and, most importantly, these adolescents have delayed access to effective therapies. To facilitate earlier access to investigational and approved drugs for adolescent patients with cancer, and because drug exposure is most often similar in adolescents and adults, we recommend the inclusion of adolescents (ages 12–17) in disease- and target-appropriate adult oncology trials. This approach requires careful monitoring for any differential safety signals, appropriate pharmacokinetic evaluations, and ensuring that ethical requirements are met. Inclusion of adolescents in adult oncology trials will require the cooperation of investigators, cooperative groups, industry, institutional review boards, and regulatory agencies to overcome real and perceived barriers. *Clin Cancer Res; 23(1); 9–12. ©2016 AACR.*

Introduction

The majority of pediatric patients with cancer are enrolled in clinical trials; however, enrollment has been shown to decrease with age, and only 10% to 15% of older adolescents (ages 15–19) with cancer participate in clinical trials (1–4). Lack of access to relevant trials for adolescents, either in the upfront or relapsed setting, is often cited as one reason for this discrepancy (5). Much of the more than 50% decrease in overall childhood cancer mortality since 1975 has been attributed to clinical trial participation, but survival improvements for adolescents and young adults have historically lagged behind the pediatric population as a whole, and decreased participation in clinical trials may contribute to this finding (6, 7). Recent reports suggest an improvement in mortality for adolescent and young adult patients with cancer as a whole, but disparities for certain histologies remain (8, 9). The types of cancers (classified by histology and/or molecular drivers) that occur in younger pediatric versus adult patients are generally very different and require different therapeutic regimens. However, some of the more common cancers in adolescent patients are similar to those seen in adults, including some soft tissue and bone sarcomas, central nervous system tumors, leukemias and lymphomas, and melanoma (10). Regardless, adolescents are generally not eligible for enrollment in clinical trials for adults that evaluate drugs with relevant mechanisms of action for either the histology or molecular derangement(s) of their cancers. Pediatric trials evaluating these drugs, even for the same disease, are often performed years later and, many times, after the drugs have been approved in adults. This delay in evaluation has several consequences: Accrual to pediatric trials evaluating drugs already approved in adults may be seriously threatened by "off-label" use in children; there are no prospectively collected data in product labeling to guide the prescribing physician on safe and effective use of the drug in adolescents at the time of adult approval; and, most importantly, the current approach contributes to delayed access to investigational and effective approved drugs for adolescent patients with more "adult-type" cancers.

To improve the expeditious access to relevant investigational drugs for adolescent patients with cancer, we recommend that sponsors consider the inclusion of adolescents (ages 12–17) in disease- and/or target-appropriate adult oncology clinical trials at all stages of development. The decision to enroll adolescents in adult trials should be based on either the histology under investigation where the biology of the tumor in adults and adolescents is felt to be the same or the molecular target of the drug where both the mechanism of action of the drug and the molecular derangement of the tumor are relevant. Drug exposure in adolescent and adult patients has been shown to be similar (11), and dosing strategies for adolescents in adult trials are discussed below. For late-stage activity-estimating or confirmatory trials, where a dosing regimen has been established in adults, adolescents can be enrolled to the trial simultaneously with adults. In very early-stage trials, which generally enroll a refractory patient population, when the biologic rationale is particularly strong, adolescents may be enrolled when criteria under 21 C.F.R. 50, Subpart D (Additional Safeguards for Children in Clinical Investigations) are met, as

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discussed below. Safety data collected during the trial should be examined for any age-related differences. The evaluation of developmental toxicities (i.e., growth derangements, fertility issues) that require a long duration of follow-up are generally not possible in the context of early-phase trials but should be evaluated in trials enrolling patients in earlier lines of therapy. When appropriate, pharmacokinetic studies should also be conducted in the adolescent population to detect any differences between the populations.

The pharmacologic basis, ethical considerations, and potential barriers to this approach are discussed below.

Clinical Pharmacology

The inclusion of adolescents in adult oncology clinical trials relies on identification of dosing in adolescents that is expected to result in drug exposure similar to exposures predicted or observed in adults at the proposed dose. Historically, starting doses for investigational therapies in phase I pediatric oncology trials have been 80% of the MTD identified in adult trials. The main objectives of these early pediatric trials are to establish the MTD in the pediatric population, identify dosing for evaluation in later phase trials, and provide assessment of the toxicity profile and pharmacokinetics of the investigational therapy in the target age group.

Several reviews have compared pediatric and adult dosing for anticancer small molecules and therapeutic proteins. Initial reviews were limited to cytotoxic drugs typically administered as single agents. In a 2005 review from the Children's Hospital of Philadelphia, the MTDs of adult and pediatric trials for 36 single-agent cytotoxic and eight biologic agents were compared (12). The MTD in children ranged between 80% and 160% of the MTD established in adults for greater than 80% of trials. Similarly, in a review focused on molecularly targeted agents, a strong concordance between the recommended phase II dose (RP2D) in children and adults was shown, with the pediatric RP2D between 90% and 150% of the approved dose or RP2D in adults (13).

Over the last several decades, there has been a significant increase in the understanding of age-related changes in drug disposition in pediatric patients (14, 15). Differences in pharmacokinetics between pediatric and adult patients are primarily due to differences in size and maturation; however, other factors, such as the relative role of pharmacogenetics, differential impact of the disease on organ function, and drug interactions, should be considered. Elimination clearance is a major determinant of dosing. *In vitro* and *in vivo* studies have shown that most elimination pathways are mature and reach adult levels by the age of 2 years (16, 17). Moreover, the clearance of drugs and many therapeutic proteins has been shown to be similar between adolescents and adults once the effect of body size on pharmacokinetics is taken into account (18, 19).

Allometric scaling is the most widely used method to establish how drug clearance and dose relate to body weight. Allometry describes the relationship of body size to a parameter of interest in the fields of physiology, ecology, paleontology, and pharmacokinetics (20). In pharmacokinetics, it relies on the principle that metabolic components of clearance correlate with the same factors that drive metabolic rate; that is, the relationship between clearance in children and body weight is not linear and is best described by a power function or exponent of $^3/_4$:

$$CL_{ped} = CL_{adult} * \left(BW_{ped}/BW_{adult}\right)^{3/4}$$

In a 2013 review from the FDA, clearance in adolescents was compared with clearance in adults for 27 drugs (11). The observed clearance in adolescents averaged 88.6% and 95.1% of the adult clearance for intravenously and orally administered drugs, respectively. A positive correlation was found between allometry-predicted and observed adolescent clearance values for intravenous and oral products with an r^2 value of 0.97. Drug dosing in adolescents and adults was also compared for 92 products with the same indication for the two populations. Of these 92 products, 87 (94.5%) had identical adolescent and adult dosing, suggesting that adolescent doses may be able to be derived using adult data. Although there may be differences in assigning a specific age range to adolescence, the findings of nearly identical doses in patients aged 12 to 17 and adults in the FDA study provide a scientific rationale and biologic justification from a pharmacokinetics perspective that adolescents aged 12 to 17 can be included in select adult trials.

In summary, sufficient data exist to support the derivation of adolescent dosing from data in adults when the objective is to match adult systemic exposure. As mentioned above, once body weight or body size is taken into consideration, drug disposition in adolescents is similar to adults; therefore, in general, the adult doses would be expected to achieve similar systemic exposures in adolescents. For drugs with body weight–adjusted dosing in adults (mg/kg or mg/m^2), the same dose can be used in adolescents. For drugs with fixed dosing in adults, a minimum body weight threshold in adolescents may need to be defined to receive the same adult dose to prevent exceeding target adult exposures. One strategy for dosing adolescents below this minimum weight is mg/kg or body surface area (BSA)-based dosing using allometry or a reduced fixed dose that will approximate dosing by allometry, depending on the flexibility of the formulation. Another approach is to scale the dose from adults by normalizing based on BSA. This approach is commonly used in clinical practice for dosing cancer therapeutics and provides a reasonable estimate for dosing in adolescents. In general, limited data are available on the pharmacologic implications of physiologic changes associated with obesity in adolescents. As a result, there is no systematic and widely accepted approach to determine which body weight (e.g., ideal body weight, total body weight, or adjusted body weight) or what cap of calculated BSA to use for dose calculation of cancer therapeutics in adolescents. Regardless of the approach, sparse sampling for pharmacokinetic assessment in adolescents should be incorporated within the adult trials to confirm pharmacokinetic predictions and to assess the need for dose optimization in obese adolescents. For drugs with a narrow therapeutic index or nonlinear pharmacokinetics, pharmacokinetic assessment prior to enrolling adolescents in large efficacy trials may be considered. This can be accomplished as a separate trial or, preferably, in a lead-in phase to larger efficacy and/or safety trials.

Ethical Considerations

FDA-regulated clinical trials that enroll adolescents with cancer must comply with the Additional Safeguards for Children in Clinical Investigations found at 21 C.F.R. 50, Subpart D. Because of the risks associated with oncology drug treatment, pediatric studies must be evaluated under 21 C.F.R. Sect. 50.52, Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects. Such studies "may involve children as subjects only if. . . (a) The risk is justified

by the anticipated benefit to the subjects; (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and (c) adequate provisions are made for soliciting the assent of the children and permission of their parents...."

Establishing a sufficient prospect of direct benefit to justify the risks requires prior information from either animal or adult human studies. The data necessary to enroll adolescents include verification through mechanistic and/or animal studies that the drug is expected to have activity against the adolescent's disease, selection of a starting dose that is expected be therapeutic, and ensuring that the duration of the study is sufficient to anticipate a therapeutic effect of the drug (if the drug is indeed effective). As such, enrolling adolescents in the earliest dose-escalation cohorts may not be supportable under 21 C.F.R. Sect. 50.52. Some drug doses and/or exposures in these studies may be subtherapeutic, and there may be little safety data upon which to base a risk–benefit assessment. The requirements of 21 C.F.R. Sect. 50.52 also necessitate that the prospect of direct benefit is sufficient to justify the risks. The known and potential unknown risks of the investigational product must be carefully assessed to support the judgment that the prospect of direct benefit justifies these risks. The regulations also require that the relation of the anticipated benefit of the investigational product to the risks of that agent is at least as favorable to the enrolled adolescent as any available (evidence-based) alternatives. For all of these reasons, the patient population selected for the trials, including the disease and stage, is crucial to an appropriate risk–benefit evaluation under Subpart D.

Once there is sufficient information to meet the above criteria, the enrollment of an appropriately selected adolescent population should proceed without further delay. There are rarely ethical barriers to the enrollment of adolescents in late-stage adult oncology trials, as sufficient information is typically available from earlier phase trials to support a sufficient prospect of direct benefit, to select a starting dose and duration of exposure that may be expected to confer benefit, and to provide preliminary safety information. In circumstances where the biologic rationale, based either on very early clinical or nonclinical data, for the use of the drug is particularly strong, it may be appropriate to enroll adolescents in early-phase trials, provided they are designed to confer a therapeutic benefit.

Potential Barriers

Some of the potential barriers, real and perceived, to expanding enrollment to adolescents in adult oncology trials are logistic, regulatory, and cultural. The logistic concerns include the location of care for the adolescent patients and require increased cooperation between pediatric and medical oncologists (and their respective institutions) who may not be in the same geographic location (5, 21, 22). Revising age eligibility criteria would also allow for the enrollment of adolescents in relevant clinical trials when they are managed outside of a pediatric setting. Issues related to clinical trial activation in pediatric and adult hospitals and with multiple institutional review boards (IRB) may be addressed with the use of central IRBs and increased collaboration between pediatric and adult clinical trial networks (9, 21, 23).

Perceived regulatory barriers relate to the need for additional preclinical studies prior to the treatment of pediatric patients, safety concerns related to the enrollment of pediatric patients in adult trials, and ethical issues. We believe these issues are surmountable. Consistent with the ICH S9 guidance, the FDA does not always require juvenile animal studies prior to the initiation of pediatric assessment of a drug (24, 25). Juvenile animal studies may be warranted when the known mechanism of action of a drug is likely to cause developmental toxicities or when available clinical or nonclinical data are not sufficient to provide information on relevant toxicities but are not routinely needed prior to the evaluation of oncology drugs in pediatrics. Developmental toxicities are less likely a concern in adolescents, and with adequate safety measures in place, including dosing recommendations and consent issues discussed above, the enrollment of adolescents in adult oncology trials is justified given the severe and life-threatening nature of their disease.

The evaluation of drugs for rare cancers, including pediatric cancers, requires global cooperation and the European experience with and support for lowering the age for enrollment on adult trials has been published (26, 27).

Finally, a culture shift will be required for investigators, pharmaceutical companies, IRBs, and regulators in adopting this approach that diverges from the traditional paradigm of pediatric drug development, which is isolated from, and often follows, drug development in adults. Early integration of the development programs of relevant drugs for both adults and adolescents will assure more timely access to effective therapies and earlier assessment to guide safe and appropriate use of drugs in adolescents.

Conclusions

The enrollment of adolescents in specific disease- and molecular target-appropriate clinical trials conducted in adults is not envisioned as a wholesale shift in the evaluation of new investigational agents in children, as strong physiologic and scientific justifications for pediatric-specific development plans exist. In addition, this approach should not delay what could otherwise be a dedicated drug development program in pediatrics. However, given the similarities in drug exposure, the enrollment of adolescents with cancer in relevant adult trials can provide more timely access to innovative therapies in the setting of life-threatening diseases under appropriate regulatory and safety oversight from which meaningful data can be derived to inform safe and effective use of a new drug.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The opinions expressed are those of the authors and should not be interpreted as the position of the FDA.

Authors' Contributions

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