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Lack of value of juvenile animal toxicity studies for supporting the safety of pediatric oncology phase I trials

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ABSTRACT

Toxicity studies in juvenile animals (JAS) are sometimes performed to support clinical trials in pediatric oncology patients, and there are differing conclusions on the value of JAS for pediatric drug development. This manuscript provides a review of the pediatric clinical data for 25 molecularly-targeted and 4 biologic anticancer therapeutics. Other publications that evaluated the value of JAS in pediatric drug development focus on differences in toxicity between juvenile animals and adult animals. The present paper examines pediatric-specific clinical findings to focus on dose setting in pediatric oncology patients and safety monitoring in terms of the potential value of JAS. Our assessment demonstrates that pediatric starting doses were safe for all 29 therapeutics examined in that no life-threatening toxicities occurred in the first cohort, and overall the ratio of the pediatric maximum tolerated dose (MTD) to the recommended adult dose was close to 1. In addition, the 4 serious adverse events (SAEs) that weren't detectable with standard monitoring plans for pediatric oncology trials would not have been detectable in a standard JAS. This review demonstrates that safe starting doses in pediatric oncology patients for these therapeutics could have been solely based on adult doses without any knowledge of findings in JAS.

1. Introduction

Although cancer in children is rare, it is the second most common cause of death among children aged 1–14 years in the United States, surpassed only by accidents. In 2017, estimations of cancer diagnoses in children were 10,270 and 1190 were estimated to die of the disease in the United States (Siegel et al., 2017). These numbers are likely higher since benign and borderline malignant brain tumors were not included in these 2017 United States estimates. In the UK, 1821 new cases of pediatric cancer occurred per year between 2013 and 2015, and in Germany 2056 new cases were reported in 2014 (Cancer Research UK, German Childhood Cancer Registry). Overall, pediatric cancers account for approximately 1% of the total cancer incidence in Europe (Steliarova-Foucher et al., 2004). Although much progress has been made in developing new and curative treatments for childhood cancers, there is an ongoing need to develop more effective and less toxic therapies.

Nonclinical (animal) repeated-dose toxicity studies are conducted for new pharmaceuticals to characterize toxicologic properties of these compounds. These general toxicology studies are usually performed in young adult animals, and the information from these studies is used to estimate an initial safe starting dose, to inform on appropriate clinical monitoring, and to guide dose escalation schemes. When expanding clinical development into pediatric populations, toxicity studies in juvenile animals can provide information useful for limiting the risk of experiencing adverse events in pediatric patients and may suggest additional monitoring endpoints (FDA, 2006). However, the nonclinical development of anticancer drugs is different when compared to other indications, and the ICH S9 guideline states that “studies in juvenile animals are not usually conducted in order to support inclusion of pediatric populations for the treatment of cancer.” This guidance no doubt arose from a long history of safely developing anticancer therapeutics in pediatric populations using starting doses for Phase 1 trials that were a fraction (typically 80%) of the adult dose without any juvenile animal studies (JAS) (Glaubiger et al., 1981; Marsoni et al., 1985; Smith et al., 1998; Shah et al., 1998; Lee et al., 2005). Despite this ICH S9 statement, JAS are often performed to support clinical trials in pediatric oncology patients.

There has been ongoing debate in the literature regarding the value of JAS for pediatric drug development in general (Baldrick, 2010; Baldrick, 2018; Bailey and Mariën, 2009; Bailey and Mariën, 2011; Tassinari et al., 2011; Soellner and Olejniczak, 2013). In addition, the value of JAS has been specifically analyzed for supporting pediatric development of oncology therapeutics. A publication by Duarte (2015)

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surveyed oncology therapeutics approved by the European Medicines Agency (EMA) from 2007 to 2014 and found 17 therapeutics for which JAS results were described in either the Summary of Product Characteristics (SmPC) or European public assessment report (EPAR). Duarte's analysis of these 17 cases identified 6 therapeutics for which different, enhanced, or unexpected toxicities were noted between juvenile and adult animals and concluded that this knowledge provided value with respect to overall safety assessment and characterization of possible risks to pediatric cancer patients. Andrews and Keller (2016) challenged this conclusion since their analysis of those 6 therapeutics indicated that the Phase 1 pediatric clinical trial designs and outcomes (i.e., starting doses and monitoring plans) would have been essentially the same in the absence of a JAS. Baldrick (2018) also questioned the utility of JAS for supporting safe administration of drugs to pediatric patients, not only in oncology, but across many therapeutic areas. This author also noted that it is unclear whether JAS findings conveyed in product labels have any impact on prescribing practices (Baldrick, 2018). Leighton et al. (2016) performed a retrospective analysis on the oncology drugs analyzed by Duarte (2015), as well as JAS submitted to the US Food and Drug Administration (FDA) in support of pediatric oncology drug development programs, in order to determine if the JAS impacted clinical trial design. These authors concluded JAS were not of value and that the starting dose for pediatric clinical trials for these therapeutics could be safely determined by using a fraction of the adult dose as has been the standard practice for decades.

Analyses of the safety of pediatric Phase 1 trials in oncology have continued to appear that include an increasing proportion of molecularly-targeted agents (Paoletti et al., 2013; Morgenstern et al., 2014; Bautista et al., 2015; Dorris et al., 2017). Paoletti et al. (2013) compared data from 19 Phase 1 pediatric trials conducted with 15 molecularly-targeted agents approved for use in adults to data obtained in the adult population. The safety profiles described in the Phase 1 pediatric trials were found to be similar to those reported in the adult population and, except for sunitinib, the recommended Phase 2 dose (RP2D) or MTD was highly concordant with the adult dose. These authors concluded that dose-finding studies (i.e., Phase 1 trials) may not be necessary for all molecularly-targeted anticancer therapeutics in children and recommended changes to the methodological approaches when designing early phase trials in this population. By inference, this conclusion indicates that JAS would also have no value if Phase 1 trials could be bypassed based on adult data.

The present paper expands on the number of drugs evaluated by Paoletti et al. (2013) and Duarte (2015). In addition, while Paoletti focused on the efficiency of Phase 1 pediatric trials based on adult data, our analysis focuses on the dose setting and safety of Phase 1 trials in terms of the potential value of JAS. Thirteen of the 25 molecularly-targeted agents covered in this manuscript were not included in the publication by Paoletti et al. (2013). Our hypothesis was that starting doses and clinical monitoring plans could have been safely implemented in the absence of JAS for all molecularly-targeted agents when adult data are available. To test this hypothesis, we reviewed the starting doses, MTDs, serious adverse events (SAEs), and dose-limiting toxicities (DLTs) from Phase 1 pediatric clinical trials for 25 molecularly-targeted and 4 biologic anticancer therapeutics approved through December 2017 and compared these data to that obtained from adults. This paper also considers the impact that data from JAS would have had on Phase 1 dose selection and safety monitoring in pediatric patients for those drugs where new safety findings arose that were not seen in adults.

2. Methods

2.1. Data

Molecularly-targeted anticancer therapeutics approved by the US FDA through December 2017 were identified, which included tyrosine kinase inhibitors, serine-threonine kinase inhibitors, histone deacetylase inhibitors, and Hedgehog signal transduction inhibitors. Biologic anticancer therapeutics were also included since they are highly targeted therapeutics that affect signal transduction. Classical cytotoxic agents (including alkylating agents, platinating agents, antimetabolites, microtubule dynamics inhibitors, topoisomerase I and II inhibitors, and RNA synthesis inhibitors) were excluded because historically these therapeutics have been successfully tested in pediatric populations based solely on adult data (Smith et al., 1998). Antiestrogens and hormonal agents were excluded because these agents are not typically indicated for pediatric cancers. PubMed, ClinicalTrials.gov, and clinical oncology meeting abstracts were searched for results from monotherapy Phase 1 pediatric trials of the identified molecularly-targeted and biologic therapeutics. Only those therapeutics with publically available Phase 1 pediatric monotherapy data were included in the analysis. Although Phase 1 pediatric monotherapy data were available for dinutuximab (ch14.18), this biologic was excluded because it is approved as combination therapy for pediatric high-risk neuroblastoma and appropriate Phase 1 monotherapy data in adults could not be identified for comparison.

2.2. Definitions

Molecularly-targeted agents were defined as small chemical entities that have a primary mechanism of action that occurs via inhibition of a signal transduction pathway. In addition, lenalidomide and the histone deacetylase inhibitors vorinostat and pabinostat, which have multiple mechanisms of action, were included in this group.

Starting doses, MTDs, and RP2Ds for the pediatric trials were extracted from the references based on the authors' assessments and adult doses were taken from the most recently approved label information (US package insert). When necessary, adult doses were normalized to body surface area (mg/m^2) using 1.7 m^2 as the average body surface area. If doses were administered on different schedules in the pediatric trial versus adults (i.e., BID vs QD), then the daily dose was used for comparisons.

Pediatric DLTs as well as other grade 3 or 4 toxicities were taken from the authors' assessments. To ensure all potential pediatric-specific adverse events (AEs) were captured, no distinction was made as to whether these adverse events occurred in the first cycle (typically used to define the MTD) or subsequent cycles. Adult adverse events were obtained from the approved US package insert, patient package insert, the EPAR, and the SmPC. Available JAS data were obtained from the FDA Pharmacology Reviews and EPARs for the therapeutics discussed.

Value for JAS studies was defined as identifying an adverse finding that was not already known from clinical development in adult humans and not part of standard monitoring programs, or identifying an increased sensitivity compared to adult animals that would have precluded using an unsafe starting dose.

3. Results

3.1. Age demographics

The youngest subjects allowed on these trials were < 1 year old for 2 drugs, 1 year old for 9 drugs, 2 years old for 5 drugs, and 3 years old for 2 drugs. Six trials did not specify the lower entry age limit (dabrafenib, imatinib, gefitinib, erlotinib, lapatinib, and lenalidomide), but it is assumed that these trials could have entered subjects < 1 year old if they met other eligibility criteria. The actual ages of subjects entered on these trials were below 2 years old for only 4 drugs (dabrafenib, crizotinib, gefitinib, and lapatinib) and the youngest subject was 1 year old (dabrafenib).