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Use of juvenile animal studies to support oncology medicine development in children

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ABSTRACT

Childhood cancer has remained a challenge because of long-term effects in children. The need to extend access of children into new cancer therapies requires early prediction of specific safety aspects and juvenile animal studies (JAS) are being conducted to screen for age-related toxicities and differences occurring during postnatal development. This paper investigates oncology approved medicines in the EU (1995–2014) and PIP (Paediatric Investigation Plans – 2007–2014), regarding the usefulness of JAS in their non-clinical development by evaluating information on the medicines labelling. The retrospective review from medicines and PIPs revealed a steady use of JAS to better characterize safety: Approximately 1 in 3 oncology medicine or PIP has conducted JAS. For 6 of the cancer medicines with JAS the toxicity profile in adult and juvenile animals showed some differences in study findings. The discussion of these cases is illustrative of the potential significance that JAS have provided in oncology medicines.

1. Introduction

Cancer is the second common cause of death in children in the developed countries [1]. Childhood cancer and its treatment have remained a challenge for oncologists and heavy burden on the child. Although many children survive cancer, they may suffer complications of chemotherapy and radiotherapy and long-term effects from their treatment [2].

The regulatory framework of clinical studies and drug development in children and adolescents with cancer are regulated by the European Directive on good clinical practice in clinical trials [3] and the Paediatric Regulation [4] published in 2006 by the European Commission, and aimed at resolving the problem of using medicines in children without the proper studies: unauthorized and off label use – for therapeutic indications, dose or posology other than the approved during the evaluation process, prior to the marketing authorization (MA).

According to this Regulation, pharmaceutical companies are obliged to propose and comply with a Paediatric investigation plan (PIP) before they can seek marketing authorization for a new medicine, to ensure that medicines that are developed for adults are also developed for children if the condition for which they are intended is relevant for the paediatric population.

It is known that different physiological and metabolic factors, pharmacokinetics and behavioural patterns can render children more or less sensitive than adults.

The need to extend the access of children into new therapies reinforces the urgency to implement strategies for early prediction of specific safety aspects in this population.

As a result of the obligation to develop medicines in children, JAS are being conducted to support applications for medicines intended for use in paediatric populations if there is a specific safety concern.

Since juvenile animals normally present developmental characteristics that could be considered similar to the paediatric population, they could therefore be considered as adequate models in the evaluation of the pharmacological effect in this population.

JAS could help to identify "unique" toxicities and age-related differences in toxicity based on the developmental process occurring during postnatal development [5], what stage of postnatal development might be more sensitive, what target organs toxicity and developmental effects could be expected [6] and whether there are any resulting consequences in the adult, to paediatric administration [7]. However, toxicity studies in juvenile animals also play a role in defining the risk for paediatric patients especially in cases

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where the potential toxicity cannot be safely or ethically monitored in patients [8].

Studies in juvenile animal models may contribute to predict whether the exposure of paediatric patients to a certain medicine can lead to potential development and/or functional deficits. Also, JAS may potentially identify toxicological signals not seen in adults, as well as possible biomarkers for clinical evaluations.

According to the ICH M3 guidance [9] the appropriateness of JAS should be considered only when previous animal data and human safety data are insufficient to support paediatric studies. One relevant species – preferably rodent – is generally considered adequate. The use of the juvenile rat, as the usual species is also confirmed in the literature [10].

The case-by-case evaluation process to determine the need for JAS as considered in European Medicines Agency [11] and Food and Drug Administration [12] guidance for the conduct of non-clinical studies in juvenile animals, includes: coverage of the clinical development windows for the intended paediatric population, target organs, adequacy of the doses to support the paediatric indication and ability to monitor safety concerns in paediatric trials, always with the aim to prevent the conduct of unnecessary JAS.

The design of JAS is flexible and will depend on the therapeutic target and age range of the patient population, results of adult human studies as well as data from previous animal studies.

Particular attention is given to non-clinical juvenile toxicology where there is a prerequisite (pharmacological class or previous knowledge) for effects on growth or when target organs are late developing, e.g. CNS, immune system, reproductive system. Further emphasis is placed on non-clinical support where paediatric plans extend to neonates and infants [13].

The data generated from these types of studies are used to improve our understanding of the potential toxicology and potential safety issues in the medicine labelling as well as guide clinical programme monitoring of key endpoints.

2. Objectives

The objective of this paper is the critical analysis of the available information of oncology medicines, regarding juvenile animal toxicity studies in their non-clinical development, to examine the contribution of these studies to the benefit-risk assessment and to evaluate this information on the labelling of the approved medicines in the European Union.

The search was performed from the following public available information:

(1) From medicines approved in oncology by Centralized Procedure (Marketing Authorization in all European Union) between 1995 and 2014.
(2) From the Paediatric Investigation Plan (PIP) authorized after the Paediatric Regulation [4] to support an oncology indication in paediatric population (2007–2014).

This retrospective review of data collected during the development of oncology medicines for children, has the aim to contribute to increase the knowledge and build up the experience on utility of JAS, in the paediatric oncology area.

3. Materials and methods

A retrospective investigation has been performed to identify and characterized the non-clinical juvenile toxicity animal studies, in the development of medicines indicated in oncology.

Marketing authorizations of all oncology medicines, approved in the European Union by the centralized procedure (1995–2014), coordinated by the European Medicines Agency (EMA) and data regarding all PIP Decisions authorized by EMA (2007–2014) were examined.

The regulatory and scientific information publicly available online by EMA website regarding European Public Assessment Report (EPAR) of approved oncology medicines [14] and authorized summaries of Paediatric Investigation Plans (PIP) Decisions for oncology medicines [15], were studied:

(1) EPAR: Reflects the scientific conclusion reached by the Committee for Medicinal Products for Human Use (CHMP) at the end of the centralized evaluation procedure regarding the benefit-risk of the medicine [14]. The annexes from each medicine's EPAR (Summary of Product Characteristics – SmPC – and Scientific Discussion), were analysed with the exclusion of the suspended or cancelled medicines (due to the inexistence of information) and the generics, biosimilars and informed consent medicines (to avoid duplication of equal information of the originator medicine).
(2) PIP Decision: Reflects the scientific conclusion reached by the Paediatric Committee (PDCO) responsible for the scientific assessment and agreement of paediatric investigation plans. The PIP aims to generate the necessary quality, safety and efficacy data through studies to support the authorization of the medicine for use in children of all ages [15]. This document reflects an agreement upon which the development and authorization of paediatric medicines should be based, including details of the timing and the measures proposed to demonstrate the quality, safety and efficacy of the medicine and in which subsets in the paediatric population [4]. In some cases, a PIP may include a waiver to study one or more age groups of children, or a deferral when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population, or when studies in the paediatric population would take longer to conduct than studies in adults [16]. PIP decisions referring to refusals and granting a waiver in all age groups were excluded; and decision agreeing on a PIP, with or without partial waiver and or deferral, were examined. The PIP modifications of an agreed PIP were only considered if new non-clinical information is added (to avoid duplication of equal information of the first agreed PIP).

In order to characterize the approved oncology medicines, the following parameters were investigated: Active substance, Anatomical Therapeutic Classification [17]; Year of approval [18]; Therapeutic indications [14] and Paediatric information (age indication, dose, contra-indication, precautions).

For the characterization of the non-clinical JAS the following parameters were considered, when available: Type of studies; animal species, age at start and duration of the study.

4. Results

4.1. Oncology approved medicines (1995–2014)

In the examined period (1995–2014) 86 medicines with oncology indication, were identified. Ten of these 86 medicines (11.6%) are specifically indicated in the paediatric population (Table 1) according to SmPC section 4.1 (*Therapeutic indications*): Temozolomide, Imatinib, Busulfan, Clofarabine, Hydroxycarbamide, Mifamurtide, Thiotepa, Denosumab, Everolimus and Mercaptopurine (indicated by approval date, from 1999 to 2012).

From these 10 medicines specifically indicated in children, 4 have been first approved for adults and the additional indication

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