nals and presented with transatlantic collaborations. The platforms may be used to develop products for all ages for a broad category of molecules for pediatric population.

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Off-patent Oral Oncology Drugs for Kids (O3K FP7-project): From bedside to PUMA

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There is an urgent need for appropriate oral formulations of anticancer drugs for the treatment of paediatric malignancies in children of all ages. The goal of the O3K consortium is to develop oral liquid formulations of cyclophosphamide and temozolomide, important chemotherapeutics which have been identified in the list of paediatric needs by European Medicines Agency (EMEA/197972/2007).

Both off-patent drugs are widely used orally for the treatment of childhood cancer. However, the currently available tablets (cyclophosphamide) and capsules (temozolomide) are not suitable for use in a paediatric setting, particularly in infants and young children, as it is often impractical for them to be swallowed. This is a major health concern since these children do not readily have direct and safe access to these curative drugs.

O3K will conduct the pharmaceutical, clinical and pharmacological studies required for the development of these oral liquid formulations. Upon completion of the project, a dossier containing data required for application for a Paediatric Use Marketing Authorisation (PUMA) will be filed for both products. O3K will provide access to curative drugs for all children with cancer, improving compliance, ensuring safety for both patient and environment and allowing the development of essential ambulatory treatments.

In accordance with ICH guidelines, the development of these agents will lead to improved quality and safety of paediatric drug formulations. The O3K project involves 9 partners (including 5 institutions and 3 SMEs providing significant expertise in clinical and pharmacological research relating to paediatric oncology along with 1 parents organisation) from three European member states (UK, Italy and France).

1. Introduction

Childhood cancers represent a rare disease accounting for less than 1% of the total number of cancer cases in humans. Across the whole of Europe, approximately 16 000 new cases of childhood cancer are diagnosed in children under the age of 19 each year. Despite the high cure rates now being achieved for certain tumour types (e.g. 80% five-year survival rates for Wilms tumour and acute lymphoblastic leukaemia), cancer remains the major cause of death from disease beyond the age of 1 year with approximately 3000 children dying from cancer each year in Europe.

During the last 30 years, access to innovative therapies developed by pharmaceutical companies has been extremely limited for children in Europe, one reason being that Paediatric Oncology does not represent a large, and hence financially attractive, area for drug marketing. In Oncology, new drugs are not usually studied at first in healthy volunteers, but in patients whose disease is refractory to all standard treatments. In children with cancer, new drugs are proposed when all the treatments known to be active in their disease have failed. Most of the anticancer drugs currently used in children have been developed by academic groups through prospective clinical trials using the drugs and formulations available for use in adults. This allowed the generation of clinical and pharmacological paediatric data for compounds that eventually went off-patent. However, there are still data missing for many off-patent oncology drugs, due to the lack of commitment by pharmaceutical companies. In particular, age-appropriate oral formulations of many important anticancer drugs have not been developed.

Oral chemotherapy is used on a daily basis to treat paediatric malignancies. Some drugs are indicated for oral use only. For example, oral temozolomide has gained popularity for the treatment of refractory brain tumours in children; 6-mercaptopurine is a major component of maintenance chemotherapy for acute lymphoblastic leukaemia. In addition, health care providers have to deal with the tablets or capsules that are available. For example, when a compound is to be given daily, the entire dose for one week is given on 4 or 5 days. In other situations, intravenous formulation may be given in the form of a drinkable solution. However, this may increase the risk of serious adverse reactions or inappropriate dosing due to poor or inconsistent bioavailability. Oral administration of anticancer drugs is a major concern in children under the age of three years. This is particularly important as paediatric malignancies in children under the age of three represent 30% of all paediatric cancers.

The O3K project will develop and evaluate new galenic formulations of two already available anticancer drug widely used in paediatric oncology with a well established safety and efficacy profile. Indeed, products, i.e. cyclophosphamide and temozolomide, have been widely used in adults and in several paediatric malignancies, with adapted posology, for many years. However, commercially available tablets and capsules are not suitable for use in all children, in particular those who cannot swallow, and among them children below the age of three. Children are not small adults. They differ from adults in development, physiology, psychology and behaviour.

There is clearly an urgent need for appropriate oral formulations that permit accurate dosing, enhance patient and compliance and improve access to safe and efficacious anticancer medicines for children, particularly in infants and very young children. There is a need to generate appropriate PK data in the entire paediatric population for cyclophosphamide, in particular when those data are not available to support current doses and schedules for children.

2. Concept and objectives

The new EU regulation on medicinal products for paediatric use (EC1901/2006) came into force on January 26th, 2007. This regulation aims to improve the health of children in Europe by:

- Stimulating research and development of medicines for use in children
- Ensuring that medicines used to treat children are appropriately tested and authorised

- Improving the availability of information on the use of medicines in children

The absence of suitable authorised medicinal products to treat paediatric diseases is an issue that has been of concern for many years. Consequently, healthcare professionals (i.e. MDs, Nurses) frequently resort to the preparation and administration of unlicensed formulations by manipulation of adult dosage forms.

The new EU regulation introduced major changes to the marketing authorisation required for patented as well as for off-patent drugs. Among them, the specific Paediatric Use Marketing Authorisation (PUMA) intends to stimulate research and development of off-patent products to improve their use in children. In particular, there is an urgent need for appropriate paediatric formulations of several oral off-patent drugs in order to allow accurate dosing, safe use and enhanced patient compliance. The needs of additional information for the use of off-patent medicines in children have been identified and listed by the EMA paediatric expert group (EMEA/197972/2007). This list includes 27 off-patent oncology products. Nine of them are oral drugs that need age-appropriate formulation.

The goal of the Oral, Off-patent, Oncology drugs for Kids (O3K) project is to develop child-appropriate liquid formulations of cyclophosphamide and temozolomide. Temozolomide (TMZ) and cyclophosphamide (CPM) are widely used for the treatment of paediatric cancer and both drugs are included in the list of paediatric needs established by the EMEA.

Two liquid formulations of cyclophosphamide and temozolomide for daily oral administration in children will be developed with the goal to further submit a Paediatric Use Marketing Authorisation (PUMA) for both compounds. This will allow the administration of the exact dose along with a good bioavailability and improved compliance at all ages.

The O3K objectives are:

- to secure the feasibility of developing the new oral formulations in terms of pharmaceutical aspects and to perform this work under the good manufacturing practices
- to perform the non clinical, clinical and pharmacological development of a drinkable suspension of temozolomide for the purpose of a submission for a Paediatric Use Marketing Authorisation in the EU
- to perform the non clinical, clinical and pharmacological development of a drinkable solution of cyclophosphamide for the purpose of a submission for a Paediatric Use Marketing Authorisation in the EU

Cyclophosphamide: a widely used drug in paediatric oncology with an increasing oral use.

Cyclophosphamide is an alkylating agent which has been used successfully to induce and maintain regressions in a wide range of neoplastic conditions, including leukaemias, lymphomas, soft tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours; such as breast and lung carcinomas. Cyclophosphamide is also used for its immunosuppressive properties in non-malignant diseases, especially autoimmune and inflammatory diseases. In oncology, oral cyclophosphasmide can be used in a palliative setting in children at a daily dose of 50 mg/m^2 and is frequently used in combination chemotherapy regimens with other cytotoxic drugs.

It is widely used in adults and children oncology at conventional schedule (French SPC Endoxan®). For oral administration in both adults and children, the doses are 100–200 mg/m^2, 1–14 days every 2 weeks or 40–100 mg/m^2 continuously.

In the UK, the oral cyclophosphamide SPC states: "The recommended dose for cyclophosphamide tablets is 50–250 mg/m^2. Cyclophosphamide tablets should be swallowed whole, preferably on an empty stomach, but if gastric irritation is severe, they may be taken with meals".

Beyond its approved indication, new doses and schedules of oral cyclophosphamide are being used in children. Oral cyclophosphamide proved to be active in combination with vinorelbine in relapsed soft tissue sarcomas as shown by a Phase II trial by the Italian paediatric sarcoma group (Casanova et al., 2004) and an ongoing confirmatory phase II trial by the French group. Oral cyclophosphamide is given at a dose of 25 mg/m^2 daily for 28 days cycles. It is believed to be active through an antiangiogenic mechanism of action (Kesari et al., 2007; Stempak et al., 2006; Orlando et al., 2006a). Sustained protracted exposure to activated metabolites is thought to be required for optimal activity. An ongoing European randomized clinical trial in high-risk rhabdomyosarcoma in children evaluates the use of a maintenance therapy, composed of vinorelbine (iv weekly) and cyclophosphamide (oral daily) for 6 months, versus no further treatment in children in complete remission after chemotherapy and surgery.

Oral cyclophosphamide is used in several so-called "metronomic" therapies in paediatric malignancies (Stempak et al., 2006), as well as in adult cancers (Kesari et al., 2007; Orlando et al., 2006b).

The efficacy of the combination of vinorelbine and cyclophosphamide (protracted oral low dose cylophosphamide) in relapsed paediatric sarcomas (41% response rate in 17 patients) (Casanova et al., 2004) has been confirmed in a large prospective phase II trial of 114 evaluable patients with relapsed or refractory malignant solid tumors. The overall response rate was 20% with complete and partial responses observed in 18/50 RMS (36%), 1/7 undifferentiated sarcoma, 2/15 Ewing, and 1/15 neuroblastoma (Oberlin et al., 2010).

A pan European phase III trial run by the European Pediatric Soft Tissue Sarcoma Group (EpSSG) was launched in March 2005 and is ongoing. Oral low-dose cyclophosphamide has been combined with zoledronic acid in a phase 1 trial in neuroblastoma patients (Russell et al., 2010). In addition, oral low dose cyclophosphamide has been combined with various agents within metronomic chemotherapy protocols in relapsed pediatric malignancies (André et al., 2008), paediatric brain tumours (Choi et al., 2008) and in children with newly diagnosed malignancies in low-income countries (Fousseyni et al., 2011).

A prospective phase II trial (SFCE-METRO 01; EUDRACT 2010-02179281) has been launched in 2010 in France to explore a combination of low dose cyclophosphamide with celecoxib, methorexate and vinblastine. In addition, the role of cyclophosphamide has been further established in pediatric non-malignant diseases such as nephrotic syndrome (Azib et al., 2011) and lupus nephritis (Baskin et al., 2010).

This confirmed the expanded use of oral cyclosphosphamide in children with malignant and non-malignant diseases and the need for an age-appropriate formulation.

As oral cyclophosphamide is only available as 50 mg tablets, variations in patient age and body weight mean that the daily dose of 50 mg/m^2 cannot be delivered accurately to many children. Clinical practices to deal with these dosing issues are not easy to standardize, and heterogeneity of exposure to the drug from one patient to another may impact on the effectiveness of treatment. For example, the exact total dose for an entire week is often given over only 3 or 4 days of treatment. This may jeopardize the efficacy of cyclophosphamide when we consider that sustained exposures to active metabolites are required for optimal activity.

Beyond the inappropriate available dosages, tablets are not suitable for children who cannot swallow, especially problematic in children less than 3 years of age. Although solutions to problems relating to its oral administration in children have been sought by some hospital pharmacists, in the form of in-house preparations

of cyclophosphamide, these only serve as a short-term solution to the problem and have clear limitations. Capsules can be made at appropriate dosages from the active principle powder as this is stable for 70 days when manufactured in 10 and 25 mg capsules (Bouligand et al., 2005). However, these capsules cannot be prepared in each hospital taking care of children with cancer as it requires specialist pharmaceutical equipment. In addition, there is still a need to open the capsules for children who cannot swallow them. Cyclophosphamide IV formulation may be used as a liquid alternative for oral administration. However, it is stable for only 14 days at +4 °C in glass containers protected from light (Paci. in-house personal review; Beijnen et al., 1992) and the bioavailability of these in-house preparations is unknown.

As such, a major goal of the project is to develop child-appropriate oral liquid formulation of cyclophosphamide. The intent is to improve oral treatment for children with cancer who are due to receive protracted daily administration of cyclophosphamide in children.

A cyclophosphamide IV dosage form (Endoxan®) is available at 20 mg/ml. This IV dosage form is widely used orally in children (off label use) with a good acceptability. Using cyclophosphamide is safe for the environment since this is an inactive pro-drug that requires liver enzymatic by CYP450 to generate alkylating moieties.

Then, we propose to develop a drinkable solution of cyclophosphamide, with an easy and fast reconstitution with the following objectives:

- to develop a drinkable solution allowing easiness of use and flexibility of administration doses depending on the age and body surface of kids
- to guarantee good tolerance of the formulation using well tolerated and agreed excipients for paediatrics
- to insure physical and chemical stability during storage and use as well as relevant safety of handling and use in ambulatory treatment situations
- to control accuracy and reproducibility of doses delivery with a suitable formulation and appropriate dosing device
- to have a manufacturing process allowing industrial scale for commercial supply
- to guarantee regulatory compliance

The goal is to have appropriate physical properties of the dosage form for a reliable manufacturing process.

Depending on the critical parameters encountered (reconstitution time and physical characteristics of powder for reliable process, stability of cyclophosphamide), 4 development options are envisaged:

- A simple distribution of the API in vials together with aroma
- A dry blend formulation combining API with excipients
- A powder granulation formulation consisting in associating excipients to the API under humid conditions followed by a drying phase.
- A hydrodispersible tablet formulation having the property to dissolve immediately (within one minute) when in contact with water.

Depending on feasibility results and mainly cyclophosphamide stability in solution, the cyclophosphamide dosage form should consist in:

- A cyclophosphamide solution for multiple administrations
- Or hydrodispersible tablets of several dosage strengths leading to an oral solution when dissolved in water at the time of administration.

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Current administration practices and preferred formulations of children's medicines in Tanzania: Summary of survey findings

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1. Introduction

It is estimated that up to 8.1 million children die every year, many of them from treatable conditions (You et al., 2010). This astounding statistic is, in part, due to the lack of pediatric drug formulations for many common infectious diseases that, in turn, cause a majority of these deaths. Even when pediatric formulations do exist, their availability in clinical settings may be variable. Con-

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