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Cytotoxic agents and pediatric particularity

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Abstract

Chemotherapy has an important role in the treatment of childhood cancers and contributes largely to current therapeutic successes. However, short- and long-term toxicity must be considered. This is why it is fundamental to understand the specificities related to the pediatric field.

Keywords: Pediatric dose; Body surface area; Weight; Cytotoxics

1. Introduction

Childhood tumours grow rapidly but often regress quickly under chemotherapy to which they are particularly sensitive. Assessing the total burden of adverse health outcomes following childhood cancer was investigated in a large retrospective cohort, which demonstrated that 75% of 1,362 childhood cancer survivors treated at the same institution in the Netherlands between 1966 and 1996 had at least one adverse event. Thus, the current objectives are not only to increase the cure rates but also to reduce the after-effects [1].

One of the major problems of cancer chemotherapy is that of variability, both in terms of therapeutic response and of tolerance to treatment. Coupled with the narrowness of the therapeutic indexes, these difficulties are accentuated. Thus, requiring the highest degree of individualization of the dose. Knowledge of the relationships between dose, concentration and concentration effect is fundamental for establishing the correct dose.

The individualization of cytotoxic doses is a priori based on an estimation of individual renal elimination capacities. The doses are in fact calculated according to a morphological parameter, namely body surface area (BSA) or weight. Several calculation formulas are available based on the hypothesis of a correlation between BSA and elimination clearance. However, being particularly problematic, the estimation of the BSA can be a poor marker of elimination capacities in certain situations, particularly those linked to impaired kidney function [2].

It is important to note that most medications doses used in pediatric oncology are based on BSA. Specific information on pediatric dosing is often lacking, that why the adult equivalent dose is extrapolated on pediatric situations. However, "The child is not a miniature adult", therefore, it is inconceivable to predict the fate of a drug in children based only on adult data and extrapolation is not valid in all situations. By administering the same dose in mg/m^2 regardless of age, we result in an overdose in young children under 12 months of age [3]. BSA approaches are often validated in children weighing more than 10 kg and can be recommended for application to drug protocols for this group of patients. Below this weight, the changes in weight and BSA as a function of age are not parallel, the dosage of chemotherapeutic drugs is thus specified on a mg/kg basis.

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By calculating the dose in mg/m^2, the attitude adopted is that of a reduction of doses. This cautious approach to drug dosing in infants and young children aims to avoid excessive myelosuppression and other significant drug toxicities resulting from impaired drug elimination (decreased biliary excretion, decreased renal tubular excretion, immaturity of liver enzymes). Another case requires specific attention, it's chemotherapy in obese children. Obesity is associated with physiological changes that can alter the kinetics of cytotoxic agents and lead to a risk of overdose or underdosage [4]. Increasing fat mass alters drug distribution according to their affinity for adipose tissue and their binding to plasma proteins. For most cytotoxic agents, there is no pharmacokinetic evaluation available for the obese population. It is therefore recommended to use the weight corresponding to the ideal weight rather than the real weight of the obese patient. The goal is to avoid any risk of overdose. The ideal weight of an obese child corresponds to the weight expected for the actual height of this child as mentioned in the literature [5].

Furthermore, during intrathecal chemotherapy, it should be noted that the volume of cerebrospinal fluid at birth is 40% of the volume observed in adults. This rate is higher than that obtained by comparing weight with that of an adult. The volume is therefore correlated with age rather than weight [6].

In the treatment or prophylaxis of meningeal leukemia, for example, it has been reported that, in children, intrathecal administration of Methotrexat at a dose of 12 mg/m^2 lead to low concentrations in the cerebrospinal fluid and reduced effectiveness. While in adults the drug reaches high concentrations and becomes neurotoxic. It is therefore appropriate to adjust doses according to age and not body size. A dose adjustment table based on age is mentioned in the summary of product characteristics.

Other particularities are linked to administration; errors in the volume and dilution of medications are more frequent in children population due to the great variability in weight and size. The volume of solvent injected must in fact be adapted to the weight of the child to avoid any risk of excessive water intake. In the case of a low injected volume, the volume of the tubing must be considered so as not to compromise effectiveness through loss of active substance.

The great variability of doses required is not easily accessible. Thus, the available dosage forms remain poorly suited to children. Solutions can be provided by pharmacists thanks to compounded preparations of medications adapted to pediatric needs.

2. Conclusion

In conclusion, knowledge of pharmacokinetics and its variability in the pediatric population is essential for the optimization of individualized dosing of cytotoxic agents. These pediatric specificities should be known and must be considered when dispensing and prescribing. This specific treatment requires close collaboration between pharmacists and doctors to be in harmony with the child's needs.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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