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Original Research

Investigating the potential impact of dose banding for systemic anti-cancer therapy in the paediatric setting based on pharmacokinetic evidence

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Abstract ***Background:*** To make systemic anti-cancer therapy (SACT) preparation more practicable, dose-banding approaches are currently being introduced in many clinical centres. The present study aimed to determine the potential impact of using recently developed National Health Service in England (NHSE) dose-banding tables in a paediatric setting.

Methods: Using pharmacokinetic parameters obtained from 385 drug administrations in 352 children aged from 1 month to 18 years, treated with five drugs (dactinomycin, busulfan, carboplatin, cyclophosphamide and etoposide), individual exposures (area under the plasma drug concentration versus time curve; AUC) obtained using doses rounded according to the published NHSE tables were calculated and compared with those obtained by standard dose calculation methods.

Results: For all five drugs, the relative variation between the NHSE dose and the recommended dose (RecDose) (standard individually calculated dose) was between −6% and +5% as expected. In terms of AUC, there was no statistically significant difference in precision between exposures obtained by the RecDose and those obtained with dose banding (absolute value of relative difference 15–34%).

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Conclusion: Based on pharmacokinetic data for these five drugs, the results generated support the implementation of NHSE dose-banding tables. Indeed, inter-patient variability in drug clearance and exposure far outweighs the impact of relatively small drug dose changes associated with dose banding.

1. Introduction

Drug dosing in oncology has historically been based on the body surface area (BSA) of the patient being treated [1]. According to the theory that larger patients have a higher elimination capacity, it is assumed that these patients need to be given higher doses than smaller patients to achieve comparable drug concentrations. For many drugs, plasma drug exposure (i.e. area under the plasma drug concentration versus time curve; AUC) is related to both toxicity and efficacy [2]. However, there is little or no direct correlation between BSA and AUC for most cytotoxic drugs, especially in adults [3]. It is arguably, therefore, somewhat surprising that the majority of anticancer drugs are still dosed based on an absolute calculation from BSA. Dose banding has recently been proposed to optimise chemotherapy preparations [4,5], with ranges (or bands) of BSA, and corresponding midpoints of each band being predefined. The individual dose for a particular patient is calculated according to a single BSA value per band, usually the midpoint of the band in which the actual BSA of the patient lies. In a recent retrospective study, there was no significant difference in precision in reaching the target AUC for the AUC obtained by either dose banding or strict BSA-based dosing for 1012 adult patients treated with one of six anticancer drugs [6].

Many hospitals in England treating adult patients have now adopted a system of dose banding for systemic anti-cancer treatment (SACT), developed by NHS England's Medicine Optimisation and Chemotherapy Clinical Reference Groups [7]. In the National Health Service in England (NHSE) dose-banding system, calculated drug doses are grouped and rounded to a set of predefined doses. Each series of consecutive dose(s) is called a 'band', with the dose to which they are rounded towards being the 'banded dose'. The NHSE bands have a maximum of 6% variance from the actual dose calculated, are defined by 'measurable' drug volume rather than a dose in milligrammes, and volumes consistent with normal vial sizes have been used to minimise waste where possible. Thanks to this system, chemotherapy provision can be rationalised and drugs with sufficient long-term stability can be prepared in advance of treatment. For doses that fall within commonly used dose bands, this can help rationalise chemotherapy service provision by enabling production, within a licenced hospital aseptic unit, or procurement from external compounding units, of standardised ready-to-use products. For less common dose bands, individualised dose preparation will still be required. The main advantages of this dose-banding approach include reduced patient waiting times and improved capacity planning of pharmacy production. Additional benefits include a reduced potential for medication errors, reduced drug wastage and prospective quality control of preparations. As recommended by the NHSE Clinical Reference Group, the national dose-banding tables are to be used by Hospital Trust Pharmacy Teams to ensure a standard approach to dose banding of chemotherapy across all hospitals. The initiative is initially focused on a relatively small number of commonly used drugs and is anticipated to help the NHSE to achieve improved values through the ability to purchase standard off-the-shelf products.

Although this approach has been demonstrated to be viable in adults, in children, the issue of chemotherapy dosing is rendered even more complex by developmental changes in organ function and by the ontogeny of drug metabolism and renal excretion, in addition to other sources of variability which also exist in adults, such as pharmacogenetic differences in drug disposition [8,9]. Also, as the correlation between clearance and BSA or weight is better in children than in adults, it is important to conduct specific analyses on the acceptability of dose banding in the paediatric setting. Furthermore, protocol chemotherapy doses in paediatrics are often made on pragmatic empirical grounds, rather than on a sound pharmacological rationale, leading to the utilisation of diverse regimens, some based on BSA and others based on body weight. Of particular concern are the conversion rules from BSA-based drug dose regimens to weight-based dose regimens, as applied to the treatment of children under a certain age (e.g. less than 12 months) or under a certain weight (e.g. less than 10 or 12 kg) at seemingly arbitrary boundaries [9]. Thus, chemotherapy-dosing approaches designated for infants and young children in particular may lead to considerable inter-individual variability in drug exposure. This has recently been highlighted for the widely used anticancer drug carboplatin, with TDM approaches recommended over the variable BSA- or body weight–based dosing regimens previously employed [10].