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SHORT COMMUNICATION

Therapeutic monitoring of carboplatin dosing in a premature infant with retinoblastoma

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Abstract
Introduction Carboplatin dosing based on renal function and therapeutic monitoring have been previously shown to be beneficial in the treatment of children with cancer. However, the applicability of such approaches to the treatment of premature or newborn infants, where kidney function may change markedly with advancing gestational and postnatal age, is unknown. Diagnosis of retinoblastoma in a preterm infant provided a rare opportunity to carry out adaptive carboplatin dosing in a patient with immature renal function.
Case report A preterm female infant born at a gestational age of 32 weeks was diagnosed with bilateral retinoblastoma at 35 weeks. Carboplatin treatment with real-time pharmacokinetic monitoring was initiated on day 26 of life at an initial dose of 6.6 mg/kg. Plasma samples were obtained at specified time points and carboplatin levels quantified by atomic absorption spectrometry. Additional doses of carboplatin were determined by pharmacokinetic monitoring based on the achievement of carboplatin AUC values of 5.2–7.8 mg/ml min on three courses of treatment. Increased carboplatin doses administered on successive courses of treatment reflected a greater than twofold increase in drug clearance, from 3.4–7.1 ml/min over a 7-week period. Pharmacokinetically-guided carboplatin dosing led to the attainment of AUCs within 10% of target values on each course of treatment. The patient completed five courses of carboplatin with both tumours defined as inactive after this treatment period.
Conclusions Data obtained from studying this patient suggests that adaptive carboplatin monitoring represents a feasible and beneficial clinical approach in preterm infants or neonates.

Keywords Paediatric · Pharmacokinetics · Carboplatin · Preterm infant · Retinoblastoma

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Introduction

Carboplatin is commonly used for the treatment of many different types of childhood and adult malignancies and represents one of a limited number of anticancer drugs where information obtained from clinical pharmacology studies is used to optimise dosing. Previous studies have shown that renal function-based dosing results in the achievement of more consistent carboplatin plasma concentrations than surface area-based dosing as carboplatin is predominantly removed from the body unchanged in the urine [1]. In addition, studies showing good correlations between carboplatin exposure (area under the plasma concentration-time curve or AUC) and clinical parameters such as toxicity and response [2, 3] have led to carboplatin being dosed to defined target AUC values in many clinical protocols. We have previously carried out studies highlighting the benefits of therapeutic drug monitoring in children receiving high dose carboplatin therapy and for carboplatin dosing in anephric patients [4, 5]. An additional patient group where monitoring may be useful is infants and very young children where renal function is likely to change as the kidneys continue to develop. This may be particularly

important in preterm infants where glomerular filtration rate (GFR) increases markedly with advancing gestational and postnatal age [6], providing the potential for altered carboplatin pharmacokinetics and toxicity.

Diagnosis of retinoblastoma in a preterm infant born at a gestational age of 32 weeks provided a rare opportunity to carry out adaptive carboplatin dosing in a patient with immature renal function. Dosing over several courses of treatment allowed the monitoring of pharmacokinetic parameters such as carboplatin clearance, changes which may be associated with renal function maturation over time. These pharmacokinetic parameters were used to guide dosing, with a view to achieving target carboplatin AUC values in this patient.

Case report

A preterm female infant was born by emergency caesarean section at 31 + 5 weeks gestation due to foetal distress. Her birth weight was 1.2 kg. On day 21 she had an ophthalmic screen for retinopathy of prematurity; there were dome shaped white substantial masses with calcific appearing centres in both eyes. There was an abnormal vascular pattern around the lesion in the left eye. In view of these findings, an urgent ultrasound scan was arranged which showed echogenic masses in the fundi of both eyes. The diagnosis of bilateral retinoblastoma was made. The tumours were felt to be too large to treat with any form of local therapy. In view of the threat to her vision, a decision was made to treat her with chemotherapy despite her prematurity and a central venous line was inserted.

Due to concerns over potential toxicity with the administration of combination chemotherapy with more than one cytotoxic drug, single agent carboplatin with real-time pharmacokinetic monitoring was selected as the most appropriate therapeutic option. Treatment was started on day 26 of life at a corrected gestational age (CGA) of 35 + 3. Carboplatin was administered as a 60-min intravenous infusion, diluted in 5% dextrose, at an initial dose of 6.6 mg/kg on day 1 of treatment, i.e. equivalent to 20 mg/kg fractionated over 3 days. Additional doses of carboplatin were determined by pharmacokinetic monitoring based on achievement of a target AUC of 5.2 mg/ml min. The ideal target AUC equivalent to the standard dose of carboplatin used to treat retinoblastoma in children (600 mg/m^2) is 7.8 mg/ml min. Due to the prematurity of the infant and the unknown tolerability of chemotherapy in this situation the target AUC for the first course of chemotherapy was reduced by 33% to 5.2 mg/ml min. Domperidone was prescribed due to vomiting but otherwise chemotherapy was well tolerated with no neutropaenia, thrombocytopaenia or episodes of sepsis.

She was re-examined before her second course of chemotherapy 3 weeks later. Her disease was found to be stable, although a further peripheral deposit was noted which may have been missed on original examination. Due to the lack of toxicity observed on course 1 of treatment, the target carboplatin exposure was increased to an AUC of 7.8 mg/ml min. The second course of chemotherapy was initiated at 38 + 4 CGA, 6 weeks and 5 days of age, with an initial carboplatin dose of 11 mg, based on carboplatin clearance observed on the previous course of treatment. Additional doses of carboplatin were determined by pharmacokinetic monitoring in order to achieve a cumulative AUC of 7.8 mg/ml min.

At term +11 days she was examined under anaesthesia. The disease had responded, but five lesions were identified and treated with laser therapy. Her third course of chemotherapy was started at term +18 days. As she had reached term, a decision was made to treat her with standard dosing for infants. This was to give 50% of the standard 600 mg/m^2 (100 mg/m^2 each day for 3 days), equivalent to 7.5 mg/kg, with a view to obtaining a target AUC of 7.8 mg/ml min. An initial dose of 20 mg was administered on day 1 of treatment and additional doses were again determined by pharmacokinetic monitoring in order to achieve an overall AUC of 7.8 mg/ml min. She became neutropaenic and suffered a septic episode on day 18 of this course of chemotherapy.

Doses of carboplatin were calculated for courses 4 and 5 in the same way as for course 3 but no pharmacokinetic monitoring was carried out. The patient completed a total of five courses of chemotherapy and at the end of this treatment the tumours in both eyes were thought to be inactive and treatment was stopped.

Pharmacokinetics and dose adjustment

Blood samples (2 ml) for pharmacokinetic analysis were obtained from a central venous line prior to carboplatin infusion, 30 mins after the start of infusion, at 60 mins (end of infusion), and at 120 mins after the start of infusion (60-mins post-infusion). All samples were taken from a different lumen to that used for drug administration. Plasma was separated from whole blood samples by centrifugation (1,200*g*, 4°C, 10 min) and 1 ml was then removed and placed in an Amicon Centrifree micropartition unit with a 30,000 MW cut-off (Millipore, Edinburgh, UK). This plasma sample was centrifuged (1,500*g*, 4°C, 15 min) to obtain plasma ultrafiltrate for determination of free carboplatin levels. Samples were sent by overnight courier, on dry ice and in an insulated container, to the Northern Institute for Cancer Research, Newcastle University, for analysis.

Platinum pharmacokinetic analyses were carried out by flameless atomic absorption spectrophotometry (AAS) using a Perkin–Elmer AAnalyst 600 graphite furnace spectrometer (Perkin–Elmer Ltd., Beaconsfield, UK). Free or unbound platinum levels were determined in plasma ultrafiltrates as previously described [7]. All samples were analysed in duplicate and values are expressed as the average of these measurements. Duplicate values were within 15% of each other in all cases. Intra- and interassay coefficients of variation for a quality assurance sample had to be <10% for an assay to be valid. The limit of quantification for the AAS assay was 1.0 μg/ml.

Carboplatin clearance and AUC were determined by Bayesian analysis following each dose of carboplatin using a two compartment model as previously described [8]. Dose adjustments were calculated based on the actual carboplatin clearance determined on day 1 and the remaining AUC to be achieved.

Results

The target carboplatin AUC was 5.2 mg/ml min on the first course of carboplatin treatment. Following administration of 11 mg carboplatin on day 1, a carboplatin clearance value of 3.0 ml/min was calculated and an AUC of 3.7 mg/ml min achieved. A reduced dose of 4.5 mg administered on day 2 resulted in an AUC of 1.3 mg/ml min, with a calculated clearance of 3.6 ml/min, giving a cumulative AUC of 5.0 mg/ml min, i.e. within 10% of the target exposure. As no toxicity was observed on course 1, the target AUC was increased to 7.8 mg/ml min on course 2 of treatment. Based on the results from pharmacokinetic analysis of samples on course 1, an initial dose of 11 mg was administered on days 1 and 2 of treatment course 2. Due to an increase in clearance to 5.0 ml/min, this dose resulted in a lower AUC of 2.2 mg/ml min on each of days 1 and 2 and an increased dose of 16 mg was administered on the remaining day of treatment. This increased dose resulted in an AUC of 2.7 mg/ml min on this additional day of treatment, with a calculated carboplatin clearance of 5.9 ml/min. The cumulative AUC was 7.1 mg/ml min, again within 10% of the target value for this course. On course 3 of treatment an initial dose of 20 mg was administered on day 1, resulting in an AUC of 2.8 mg/ml min following another increase in carboplatin clearance to 7.05 ml/min. A further dose of 20 mg was given on day 2, with a reduced dose of 15 mg on day 3, resulting in AUC values of 2.8 and 2.1 mg/ml min, respectively with a consistent carboplatin clearance of 7.1 ml/min. This resulted in a cumulative AUC of 7.7 mg/ml min over the 3 days of treatment (target AUC 7.8 mg/ml min). A summary of carboplatin doses and AUC values for each course of treatment is shown in Table 1.

Mean carboplatin clearance values of 3.4, 5.6 and 7.1 ml/min were determined on courses 1, 2 and 3 of treatment, respectively. These values represent 1.6- and 2.1-fold increases in clearance on courses 2 and 3, respectively as compared to those determined on course 1 of treatment, over a period of 7 weeks (Fig. 1). Available information relating to patient renal function was limited to serum creatinine levels of 51, 43 and 43 μmol/L on day 1 of treatment courses 1, 2 and 3, respectively.

Haematological toxicity was not observed following the first or second courses of carboplatin chemotherapy (achieved AUC values of 5.0 and 7.1 mg/ml min, respectively) but a white cell nadir of 2.75×10^9/L, and a platelet nadir of 90×10^9/L, were observed following course 3 of treatment (AUC 7.7 mg/ml min).

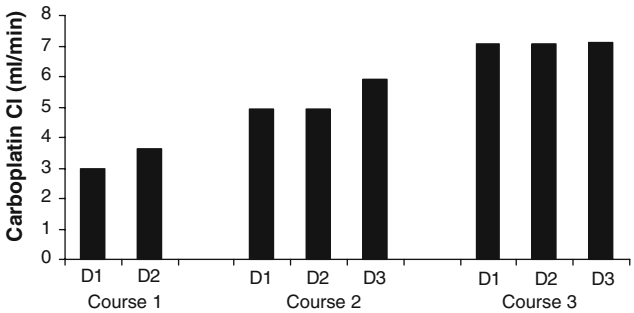

Fig. 1 Carboplatin clearance values calculated on courses 1, 2 and 3 of treatment. Carboplatin was administered as a 1-h infusion on each of 2 days (course 1) or 3 days (courses 2 and 3) of treatment

Table 1 Carboplatin treatment and target and actual AUC values obtained on all courses of treatment

Carboplatin course	BW (kg)	Target AUC (mg/ml min)	Actual dose (mg)				AUC (mg/ml min)			
			Day 1	Day 2	Day 3	Total	Day 1	Day 2	Day 3	Total
1	1.6	5.2	11	4.5	–	15.5	3.7	1.3	–	5.0
2	2.3	7.8	11[a]	11	16	38	2.2	2.2	2.7	7.1
3	2.7	7.8	20	20	15	55	2.8	2.8	2.1	7.7

BW Body weight

[a] Day 1 dose based on carboplatin exposure on previous course of treatment

Discussion

Kidney development occurs from week 3–5 gestation but is not complete until 34 weeks gestation. In utero the function of the kidneys is to maintain the volume of fluid in the amniotic cavity rather than to maintain biochemical homeostasis. After birth the kidney must adapt to conserve water, excrete waste products of metabolism and regulate acid base and electrolytes. These functions are dependent on glomerular filtration and tubular reabsorption and secretion [9]. Infants less than 34 weeks gestation have an underlying immaturity of glomerular filtration until nephrogenesis is complete [10]. At less than 30 weeks gestation, the GFR is less than 10 ml/min/1.73 m^2, which in adults would require dialysis [11]. There is then a steepening, almost exponential increase, in GFR with gestational age from 26 until 34 weeks [12]. The kidney of the newborn has a very low GFR due to low mean arterial pressure and high intravascular resistance. This is sufficient for normal growth and development, but provides only limited adaptation to a stressful catabolic state, such as is common in sick preterm infants. GFR approximately doubles during the first 2 weeks of life in both term and preterm infants, irrespective of changes in weight, due to an increase in mean arterial blood pressure, renal blood flow, glomerular permeability and filtration surface area [12].

These physiological changes provide challenges for the prescriber when treating infants, but this is particularly the case in the face of prematurity. Chemotherapy doses are generally established after carrying out phase I dose finding studies in adults and in some cases also in children. However, no such studies have been carried out to determine maximum tolerated doses of carboplatin or other anticancer drugs in full-term or premature infants. Administration of single agent carboplatin to a preterm infant presenting with retinoblastoma provided a rare opportunity to investigate pharmacokinetic variation and to use the information obtained to positively impact on the treatment received. Pharmacokinetically-guided carboplatin dosing in this patient led to the attainment of AUCs within 10% of target values on each course of treatment. Target AUC values were defined based on a previous knowledge of carboplatin pharmacokinetics in children and the toxicity observed in the preterm infant patient following each course of chemotherapy. The benefits of this pharmacokinetic monitoring approach to treatment are highlighted by the observed two-fold increase in carboplatin clearance over a relatively short 7-week period following course 1 of treatment, necessitating the administration of significantly increased doses of carboplatin on subsequent courses. While an increase in GFR might be predicted over this time period, the magnitude of these changes and the implications for carboplatin dosing have not previously been investigated. As only limited information relating to renal function was available for this patient, it was not possible to investigate a direct correlation between carboplatin clearance and development of kidney function. However, such investigations are warranted in future patients.

It is hoped that this information will provide a useful tool to guide the future treatment of preterm infants with carboplatin. Data obtained from studying this patient suggests that adaptive carboplatin monitoring represents a feasible and beneficial clinical approach in this setting.

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