Institution: Newcastle University

Unit of Assessment: UoA1

Title of case study: Optimising the treatment of childhood cancer through therapeutic drug monitoring

Summary of the impact

Clinical pharmacology studies conducted at Newcastle have led to optimisation of the administration of the chemotherapy drug carboplatin in children with neuroblastoma and other cancers. The research provided the rationale for carboplatin dosing based on patient renal function, with individualised dosing resulting in increased drug efficacy and reduced toxicity. This approach is now in widespread use in national and European treatment protocols, benefitting over 2,500 children. Similar drug monitoring approaches are being implemented for an increasing number of important drugs. Following a recent Newcastle-led national clinical trial, new dosing guidelines for the drug 13-*cis* retinoic acid have been adopted for high-risk neuroblastoma patients across Europe.

2. Underpinning research

Key Newcastle researchers
(Where individuals left or joined the university in the period 1993-2013, years are given in brackets)

AV Boddy (1998 onwards), lecturer/senior lecturer 1998-2006, then Professor of Cancer Pharmacology; AH Calvert (1990-2009), professor of medical oncology; DR Newell, professor of cancer therapeutics and senior pharmacologist; ADJ Pearson (1989-2005), Professor of Paediatric Oncology; GJ Veal (1998-onwards) research associate/senior research associate 1998-2005, research fellow 2005-2010 then lecturer/senior lecturer.

Background

Cancer is the leading cause of death from disease in children aged 1-14 years of age, accounting for approximately 20% of all deaths in this age group in the UK. Neuroblastoma is the most common paediatric malignant solid tumour outside the central nervous system, with approximately 100 cases diagnosed annually in the UK and around 900 cases in Europe. The median age at diagnosis is 22 months and the most common type of neuroblastoma is high risk neuroblastoma. This is incurable in over 50% of cases, which in the UK accounts for approx. 15% of cancer related deaths in childhood.

The platinum agent *cis*platin has been used since the 1970s as a chemotherapeutic drug. Whilst highly effective in the treatment of neuroblastoma and other childhood cancers, the associated long-term toxicity and side effects, including hearing loss (Brock et al. 2012, PMID: 22547603) and kidney damage (Skinner et al. 2009, PMID: 19850470), have encouraged the development of less toxic platinum analogues, leading to the introduction of carboplatin for clinical use. Work in Newcastle and elsewhere had led to a detailed understanding of the pharmacokinetics (the fate of a drug from administration to the point when it is eliminated from the body) of carboplatin in adults. However, there were essentially no data available in children on the pharmacokinetics of carboplatin, a drug used in induction and consolidation chemotherapy regimens for intermediate and high-risk neuroblastoma, when Newcastle initiated these studies [R1].

Research

The Newcastle group identified two key factors relevant to carboplatin-treatment in children. Firstly, removal of carboplatin from the body was shown to be almost exclusively via elimination of unchanged drug in the urine, with drug clearance found to be closely related to the glomerular filtration rate of the patient. Secondly, exposure (a pharmacokinetic measure that is derived from the drug concentration in the blood and the time it remains in the body) to carboplatin was shown to be more closely correlated than dose of drug administered to both toxicity and clinical response (reduction in tumour size) [R1]. In order to improve standard clinical practice and achieve target drug exposures, Newcastle researchers devised equations to determine the most appropriate carboplatin dose to be administered to individual patients; producing dosing tables and developing appropriate blood sampling strategies to facilitate the monitoring of drug levels in patients [R1, R2]. Subsequent research led by Newcastle, as part of a national multi-centre study, demonstrated in a

randomised controlled trial that dosing patients according to renal function resulted in more uniform drug exposure drug [R3]. This ground-breaking research led to a shift from conventional dosing based on body size or surface area to a more rational individualised dosing approach based on renal function. This is particularly pertinent in a paediatric setting, since there is significant variation in renal function throughout childhood.

Further studies on methods for estimation of renal function in children and the impact of total nephrectomy (kidney removal) and dialysis (removal of waste from the blood) on the elimination of carboplatin [R4] have allowed the drug to be administered safely in a variety of challenging clinical settings. Perhaps most importantly, using a combination of renal-function estimation and therapeutic drug monitoring, where concentrations of the drug are measured in plasma to inform future dosing de*cis*ions, the Newcastle group has pioneered an approach to the safe use of high-dose carboplatin for resistant tumours [R5].

Since the carboplatin dosing approach was established, similar therapeutic drug monitoring studies have been carried out with 13-*cis* retinoic acid (13-*cis*RA) [R6]. This is a key drug used in maintenance treatment for high-risk neuroblastoma patients. Recently published data from a Newcastle-led national study indicated that children who weigh less than 12kg, who receive a reduced dose of 13-*cis*RA, are more likely to experience sub-therapeutic drug exposures and therefore may be less likely to benefit from treatment [R6]. In addition, children who are unable to swallow 13-*cis*RA capsules whole due to their young age, for whom the drug has to be extracted and mixed with food, are also at risk of experiencing low drug exposures [R6].

3. References to the research

(Newcastle researchers in bold. Citation count from Scopus, July 2013)

R1. **Newell DR**, **Pearson ADJ**, Balmanno K, Price L, Wyllie RA, Keir M, **Calvert AH**, Lewis IJ, Pinkerton CR, Stevens MCG. Carboplatin pharmacokinetics in children: The development of a pediatric dosage formula. Journal of Clinical Oncology (1993). 11: 2314-2323. **Cited by 104** (PMID:8246021)

R2. **Ghazal-Aswad S**, **Calvert AH**, **Newell DR**. A single-sample assay for the estimation of the area under the free carboplatin plasma concentration versus time curve. Cancer Chemotherapy and Pharmacology (1996). 37: 429-434. DOI: 10.1007/s002800050408 **Cited by 4**

R3. **Thomas HD**, **Boddy AV**, English MW, Hobson R, Imeson J, Lewis I, Morland B, **Pearson ADJ**, Pinkerton R, Price L, Stevens M, **Newell DR**. Prospective validation of renal function-based carboplatin dosing in children with cancer: a United Kingdom Children's Cancer Study Group trial. Journal of Clinical Oncology (2000). 18: 3614-21. **Cited by 36** (PMID:11054434)

R4. **Wright J**, **Boddy AV**, **Highley M**, **Fenwick J**, **McGill A**, **Calvert AH**. Estimation of glomerular filtration rate in cancer patients. British Journal of Cancer (2001). 84: 452-459. DOI: 10.1054/bjoc.2000.1643. **Cited by 94**

R5. **Veal GJ**, **Errington J**, **Tilby MJ**, Pearson ADJ, Foot ABM, McDowell H, Ellershaw C, Pizer B, Nowell GM, Pearson DG, **Boddy AV** on behalf of the UKCCSG Pharmacology Working Group. Adaptive dosing and platinum-DNA adduct formation in children receiving high dose carboplatin for the treatment of solid tumours. Br J Cancer (2007). 96: 725-731. DOI: 10.1038/sj.bjc.6603607. **Cited by 14**

R6. **Veal GJ**, **Errington J**, **Rowbotham SE**, **Illingworth NA**, **Malik G**, **Cole M**, **Daly AK**, Pearson AD, **Boddy AV**. Adaptive dosing approaches to the individualization of 13-cis-retinoic acid (isotretinoin) treatment for children with high-risk neuroblastoma. Clinical Cancer Research (2013) 19(2):469-79. DOI: 10.1158/1078-0432.CCR-12-2225. **Cited by 1**

Key funding awards

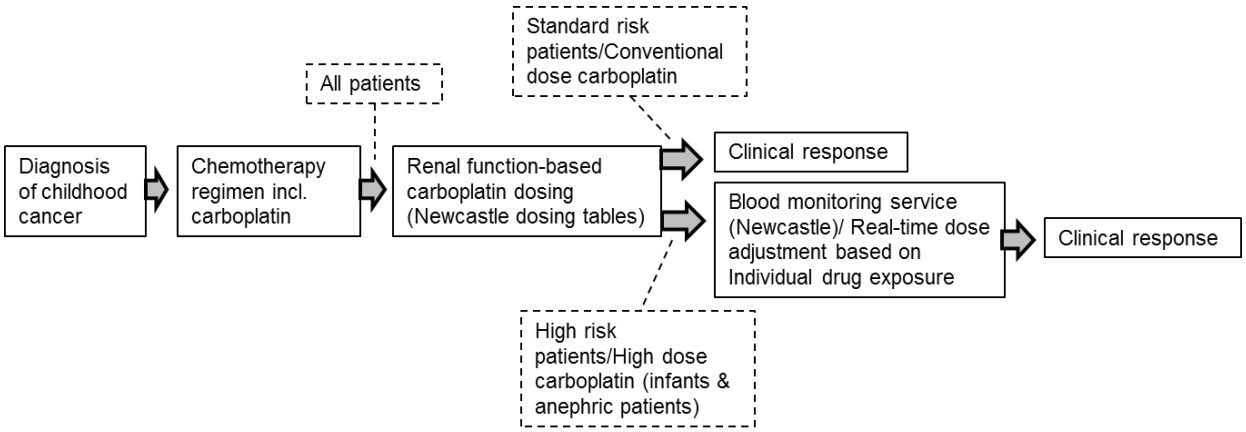
- 2000-2010 *Pharmacology Studies in Paediatric Oncology*, CRUK Programme grant - £900,000
- 2004-2008 *Pharmacology of retinoids in neuroblastoma*, CRUK PhD Studentship - £100,000
- 2005-2010 *Academic Fellowship in patient-oriented medical research*, RCUK - £125,000

4. Details of the impact

As a result of the underpinning research detailed above, Newcastle has become a leading centre for studying the pharmacology of drugs used to treat children's cancer and so has had a significant impact on the conduct of national and European clinical trials. Crucially, these trials equate to standard treatment approaches for most childhood cancers, and trial protocols act as clinical guidelines. Approximately 90% of neuroblastoma patients are enrolled in clinical trials.

Benefits to Patients treated with Carboplatin

Newcastle is now established as the national centre for pharmacology studies in childhood cancer, coordinating patient recruitment in 18 UK treatment centres [EV a]. A blood testing service offered by the Newcastle laboratory has been used routinely by 12 of the UK's major treatment centres for children with cancer since 2008, including all of the largest centres, e.g. Alder Hey, Birmingham Children's Hospital and Great Ormond Street [EV a]. The following figure graphically represents the use of carboplatin in treating neuroblastoma patients, in accordance with the protocol for the European High-Risk Neuroblastoma Trial [EV b; Trial NCT01704716] and other challenging patient populations of various tumour types. It shows how the Newcastle blood testing service, alongside the provision of dosing tables by the Newcastle group, has had a direct impact on the treatment of children with carboplatin:



The blood testing service is used to determine individualised dosing for the treatment of children with high dose carboplatin chemotherapy and other patients where drug dosing is particularly challenging, including very young children and those without functional kidneys, thus protecting them from experiencing excessive drug exposures. This is a vital tool, and one of the Consultant Paediatric Oncologists at Alder Hey hospital states that through using this service they have '*…observed the need for significant dose adjustment in several patients*' [EV c]. Furthermore, a Consultant Paediatric Oncologist at Birmingham Children's Hospital, confirms that overdosing patients with carboplatin '*…significantly increases the chances of death from non haematological end organ toxicity during these procedures*' and that '*…under dosing patients increases the chance of relapse from their malignant tumours*' [EV d]. He goes on to say that:

> '*…using the real-time Carboplatin pharmacokinetically guided dosing has allowed both reductions and increases in the predicted total dose of carboplatin of more than 20% and this service has improved both safety and efficacy for our patients*' [EV d].

A Consultant Paediatric Oncologist at Great Ormond Street also confirms that the Newcastle drug monitoring service *'…has been invaluable for the treatment of patients receiving high dose chemotherapy and infant patients where the risk of drug toxicity is a real concern*' [EV e].

Through involvement with the Children's Cancer and Leukaemia Group, the Newcastle dosing tables for carboplatin are routinely included in clinical trial protocols for various types of childhood cancer, including neuroblastoma and brain tumours [EV b]. Between Jan 2008 and July 2013 there were four open clinical trials using the Newcastle dosing tables, with an estimated enrolment of 2,400 children [EV b], all of whom benefit from a more uniform drug exposure to carboplatin. In addition, since 2008 the blood testing service has been used to guide dosing in 54 children outside of clinical trials, with dose changes implemented in approximately 75% of these patients [EV a, EV f]. Notably, the carboplatin dosage tables have been incorporated into a European High-Risk Neuroblastoma Trial (HR-NBL-1/SIOPEN), which to date has recruited over 2,000 children at 115 sites across Europe and Australia [EV b; Trial NCT01704716]. Furthermore, Newcastle provides

one of only three reference laboratories for this trial [EV b; Trial NCT01704716].

As noted in Section 2, carboplatin has important advantages over *cis*platin in terms of reduced long-term toxicity. Now, thanks to the drug monitoring approaches developed at Newcastle carboplatin-toxicity can also be appropriately controlled, even in clinical studies where high doses of carboplatin are necessary. This has ultimately resulted in improved care of children being treated for a number of tumour types. Recently, use of the Newcastle drug monitoring approach has also allowed a curative carboplatin regimen for retinoblastoma to be used safely in the context of maturing renal function in a neonate who was diagnosed with the disease at 35 weeks (gestational age) [EV f]. This highlighted a clinical situation where carboplatin therapeutic drug monitoring represented the only feasible treatment approach to ensure an appropriate drug exposure, leading to a successful treatment outcome [EV f].

Benefits to Patients treated with 13-*cis* Retinoic Acid

Since 2008, and following the establishment of the carboplatin dosing approach, the Newcastle group have been leading therapeutic drug monitoring studies for an additional 11 important chemotherapeutics [EV g]. The Newcastle-led national study on dosing of 13-*cis* retinoic acid (13-*cis*RA) in high-risk neuroblastoma patients (R6 in section 3) reported that some children are receiving potentially sub-therapeutic doses and therefore may be less likely to benefit from treatment. 13-*cis*RA is a key drug used in maintenance treatment for high-risk neuroblastoma; combining bone marrow transplantation with 13-*cis*RA treatment results in an 18% increase in 5 year survival rates compared to bone marrow transplantation alone [EV h], highlighting the clinical importance of this drug. As a result of the Newcastle findings, published online in October 2012, children weighing less than 12kg now no longer receive reduced drug doses in clinical trials across Europe [EV b; Trial NCT01704716, EV i], and recommended increased dose levels for children unable to swallow capsules have also been adopted [EV b; Trial NCT01704716, EV i]. These improved dosing guidelines have an impact on over two-thirds of high-risk neuroblastoma patients and allow for optimal administration of 13-*cis*RA across Europe, as highlighted in a recent editorial published in *Clinical Cancer Research* [EV j].

5. Sources to corroborate the impact

EV a. List of UK Centres Utilising Newcastle Real-Time Carboplatin Monitoring / Dose Adjustment Service, including patient numbers, supplied by the Blood Sampling Service (Contact provided, and list available on request).

EV b. Data and protocols sourced from clinicaltrials.gov.uk. Trial refs: NCT01704716, NCT00047138, NCT00025103 and NCT00274950

(Collated table of trials, and full protocol for NCT01704716 available on request)

EV c. Letter from Consultant Paediatric Oncologist (Alder Hey Hospital, Liverpool)

EV d. Letter from Consultant Paediatric Oncologist (clinical lead for chemotherapy) (Birmingham Children's Hospital)

EV e. Letter from Consultant Paediatric Oncologist (Great Ormond Street Hospital, London)

EV f. Picton et al. Therapeutic monitoring of carboplatin dosing in a premature infant with retinoblastoma. Cancer Chemother Pharmacol (2009) 63:749–752. DOI: 10.1007/s00280-008-0787-6.

EV g. Literature search; trials using drug-monitoring approaches for chemotherapeutic drugs other than carboplatin. Table, including references, available on request.

EV h. Matthay KK et al. Long-Term Results for Children with High-Risk Neuroblastoma Treated on a Randomized Trial of Myeloablative Therapy Followed by 13-*cis*-Retinoic Acid: A Children's Oncology Group Study. J Clin Oncol (2009). 27(7):1007-13. DOI: 10.1200/JCO.2007.13.8925.

EV i. Long Term Continuous Infusion ch14.18/CHO Plus s.c. Aldesleukin (IL-2) (LTI): http://www.clinicaltrials.gov/ct2/show/NCT01701479

EV j. Matthay KK. Targeted isotretinoin in neuroblastoma: Kinetics, Genetics or Absorption. Clin Cancer Res (2013) 19(2):311-3. DOI: 10.1158/1078-0432.CCR-12-3313