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Performance of formulae based estimates of glomerular filtration rate for carboplatin dosing in stage 1 seminoma

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Abstract ***Background:*** Single cycle carboplatin, dosed by glomerular filtration rate (GFR), is standard adjuvant therapy for stage 1 seminoma. Accurate measurement of GFR is essential for correct dosing. Isotopic methods remain the gold standard for the determination of GFR. Formulae to estimate GFR have improved the assessment of renal function in non-oncological settings. We assessed the utility of these formulae for carboplatin dosing.

Methods: We studied consecutive subjects receiving adjuvant carboplatin for stage 1 seminoma at our institution between 2007 and 2012. Subjects underwent 51Cr-ethylene diamine tetra-acetic acid (EDTA) measurement of GFR with carboplatin dose calculated using the Calvert formula. Theoretical carboplatin doses were calculated from estimated GFR using Chronic Kidney Disease-Epidemiology (CKD-EPI), Management of Diet in Renal Disease (MDRD) and Cockcroft–Gault (CG) formulae with additional correction for actual body surface area (BSA). Carboplatin doses calculated by formulae were compared with dose calculated by isotopic GFR; a difference <10% was considered acceptable.

Results: 115 patients were identified. Mean isotopic GFR was 96.9 ml/min/1.73 m^2. CG and CKD-EPI tended to overestimate GFR whereas MDRD tended to underestimate GFR. The CKD-EPI formula had greatest accuracy. The CKD-EPI formula, corrected for actual BSA, performed best; 45.9% of patients received within 10% of correct carboplatin dose. Patients predicted as underdosed (13.5%) by CKD-EPI were more likely to be obese ($p = 0.013$); there were no predictors of the 40.5% receiving an excess dose.

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Conclusions: Our data support further evaluation of the CKD-EPI formula in this patient population but clinically significant variances in carboplatin dosing occur using non-isotopic methods of GFR estimation. Isotopic determination of GFR should remain the recommended standard for carboplatin dosing when accuracy is essential.

1. Introduction

Stage 1 seminoma is the most common presentation of testicular germ cell tumour (GCT) and accounts for approximately 40% of all occurrences [1]. The management of stage 1 seminoma historically included adjuvant radiotherapy, however following orchidectomy, cases can be managed by surveillance alone or single agent carboplatin adjuvant therapy [2,3]. Carboplatin is a platinum based alkylating agent that interferes with DNA processes and is used in the treatment of several malignancies [4]. The main therapeutic and toxic effects of carboplatin are related to its cytotoxicity. The most important dose-limiting toxicity of carboplatin exposure is myelosuppression, particularly thrombocytopaenia. Carboplatin exposure, defined as the area under the plasma concentration versus time curve (AUC), is associated with both severity of toxicity and anti-tumour effect [5]. Carboplatin is mainly eliminated by the kidneys. In patients with normal renal function, approximately 60–70% of an administered carboplatin dose is excreted by the kidneys within 24 h of administration. Carboplatin clearance is poorly associated with body surface area (BSA) but has a linear relationship with glomerular filtration rate (GFR) [5,6].

The Calvert formula is widely used for dosing carboplatin and incorporates GFR as its key variable [6]. It is therefore essential to establish an accurate GFR. Clinical data are suggestive of a dose–response curve across therapeutically deliverable doses of carboplatin [4]. Consistent with these data, an exploratory analysis of the MRC TE19/EORTC 30982 study, a randomised trial comparing carboplatin with radiotherapy (RT) as adjuvant treatment for stage 1 seminoma, found a higher risk of relapse in patients where carboplatin dose was calculated based on creatinine clearance with an arbitrary 10% dose reduction applied, in comparison to those patients dosed according to isotopic GFR [3]. This highlights the importance of accurate assessment of GFR and hence carboplatin dose in this setting. In the UK current oncological practice commonly employs isotopic methods to calculate measured GFR such as the chromium-51 ethylene diamine tetra-acetic acid (EDTA) clearance method (51Cr-EDTA) [7,8]. 51Cr-EDTA is accurate, reproducible, is validated for prescription of chemotherapy, and is considered 'gold-standard' in this setting. However, it is relatively time consuming, requires access to specialised equipment (a gamma counter), nuclear medicine expertise and involves the handling and disposal of radioactive materials. Centres without access to a nuclear medicine department may experience logistical difficulties in obtaining the estimation of renal function for accurate prescription of chemotherapy.

A number of methods of deriving GFR based on estimating equations have been developed. The most widespread in routine clinical practice in the general population is the 4-point MDRD (Management of Diet in Renal Disease (MDRD)) formula, which calculates estimated glomerular filtration rate (eGFR) [9]. This formula is widely used for the diagnosis and classification of chronic kidney disease [10]. This takes into account age, gender, race (white or Afro-Caribbean) and serum creatinine. A calculated MDRD eGFR is issued with all biochemistry reports measuring the biochemical panel of urea, creatinine and electrolytes in the United Kingdom. Whilst well validated as a measure of kidney function, this formula was derived from patients with known kidney disease and has not been robustly validated in patients without renal impairment, and is generally considered inadequate for use in calculating drug dosing. In addition to kidney function, serum creatinine is influenced by other factors including diet, muscle mass (low in the elderly, cachexia and amputees) and drugs (e.g. trimethoprim impairs tubular secretion of creatinine). Whilst eGFR reporting has improved detection and management of chronic kidney disease, the MDRD formula tends to underestimate eGFR at higher levels of kidney function [11]. To address the limitations of the MDRD formula the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula has emerged to derive an eGFR, demonstrating less bias, greater accuracy and improved precision [12] and it is likely that this will be widely adopted as the standard measure of kidney function in all adult patients, following its endorsement in the most recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines [10].

The Cockcroft–Gault (CG) formula is still widely used for the calculation of renal function to guide dosing for many drugs (e.g. gentamicin). Cockcroft–Gault calculates creatinine clearance (CrCl) rather than GFR [13]. In general CrCl tends to overestimate GFR due to tubular secretion of creatinine, particularly at lower levels of kidney function. Moreover, with obese patients, who have a relatively lower muscle mass, if actual body weight is used, CG will overestimate GFR, whilst if ideal