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Harmonization on renal function assessment is needed during early clinical development of oncology drugs

Michelle A. Rudek¹, Richard A. Graham², and Mark J. Ratain³

¹The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA

²Onyx Pharmaceuticals, Inc. A subsidiary of Amgen. South San Francisco, CA, USA

³Department of Medicine, University of Chicago, Chicago, IL, USA

As with other therapeutic areas, the need to understand the disposition of antineoplastic drugs in patients who have hepatic and renal dysfunction is paramount during drug development to define the optimal dose in these special populations. While renal impairment was originally only thought to alter drugs cleared by renal mechanisms, there is now *in vitro* evidence that uremic toxins inhibit drug metabolism enzymes and transporters and clinical evidence that renal dysfunction can lead to alterations in the pharmacokinetics of drugs cleared primarily by hepatic mechanisms.¹ Indeed, it is upon this basis that the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommend a dedicated renal impairment study in patients with varying degrees of renal impairment for small molecule drugs intended for chronic use regardless of their elimination pathways (i.e., even for drugs which are eliminated by non-renal pathways).^{2,3} For drugs mainly eliminated by non-renal pathways, a reduced renal impairment study in end-stage renal disease patients can be conducted (a reduced pharmacokinetic study) in patients with severe renal impairment.⁴ However, since 2010 even the reduced pharmacokinetic study design was not conducted for several FDA-approved oncology drugs (USPI and Summary Basis for Approval Documents) and instead the label information was based upon results from population pharmacokinetic analyses. Traditionally oncology diverges from general guidance documents during the conduct of early phase clinical trials by allowing eligibility for patients with mild renal dysfunction. Oncology patients with a serum creatinine within normal limits or an estimated creatinine clearance (CrCl) of greater than 60 mL/min are often eligible for early phase clinical trials, which has led to a disconnect with the categorization of renal impairment by the FDA and the NCI's Organ Dysfunction Working Group. There is a need for harmonization of renal impairment categorization during the conduct of early phase and renal impairment trials in oncology to ensure more precise dosing recommendations.

* **Correspondence:** Michelle A. Rudek, Pharm.D., Ph.D. The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1650 Orleans Street, Bunting-Blaustein Cancer Research Bldg. Room 1M52, Baltimore, MD 21231-1000 USA. Phone: (443) 287-6476; Fax: (410) 502-0895; mrudek2@jhmi.edu.

Editorial on "Effect of renal dysfunction on toxicity in three decades of CTEP-sponsored single-agent phase I studies"

Disclosures: R.A.G. is a former employee of Genentech and is a current employee of Onyx Pharmaceuticals, Inc. A subsidiary of Amgen.

In this issue of the *Journal of Clinical Oncology*, Beumer and colleagues⁵ sought to reconcile whether there is a safety concern with cancer patients in the FDA categorization of mild renal impairment (CrCl=60 to 90 mL/min) being eligible for early phase clinical trials. The authors performed a retrospective assessment of 373 phase I studies sponsored by CTEP conducted over 3 decades (1979–2010) to determine whether patients in the FDA categorization of mild renal dysfunction experienced significant increases in toxicity, and if so the potential long-term ramifications to oncology drug development. The focus was on single-agent phase I studies at the two highest dose levels to maximize sensitivity while minimizing confounding factors. The assessment was truncated to October 2010 to limit any confounding factors imparted by the Isotope Dilution Mass Spectrometry (IDMS)-traceable creatinine conversion in CLIA laboratories. As was noted, the estimated glomerular filtration rate (GFR) increased with time, which the author attributed to the increasing weight trend during the 3 decade assessment period. In trials utilizing 179 drugs over broad therapeutic categories (e.g., biologics, cytotoxic, and molecularly targeted agents), there was a small statistical difference between the mild renal dysfunction and normal renal function and the degree of Grade 3 or 4 non-hematologic or any toxicity. The authors concluded that the 3.7% change was not significant enough to warrant adjusting how early phase clinical oncology trials are conducted and supports the use of a modified study design to only study mild renal dysfunction if there is a difference in tolerability and pharmacokinetics in the moderate and severe renal dysfunction cohorts.

We concur that the conduct of dedicated renal impairment trials is cumbersome during oncology drug development. As the authors highlight, the severe impairment category is difficult to enroll since most patients at that extreme of renal impairment are on dialysis. Indeed, an integrated assessment of the clinical pharmacology of the drug can often provide an understanding of the impact of renal impairment on pharmacokinetics and ultimately dose optimization. The assessment can include data from human mass balance, drug-drug interaction, hepatic impairment studies, and population pharmacokinetic analyses. This approach was taken with vismodegib and the package insert documents the results.⁶

While the manuscript focused primarily on the patients with renal function between the FDA categorization of normal renal function and that typically assumed in early phase trials in oncology, the authors failed to utilize the data to address larger concerns in oncology drug development. The larger concerns that could have been addressed include the enrollment of patients in phase 1 trials, despite the presence of significant renal impairment. This is evident in the larger proportion of patients (~18% of patients had a CrCl <60 mL/min by Cockcroft-Gault and ~32% had a CrCl <60 mL/min/1.73 m² by Jelliffe) who have calculated GFR values that fall within a moderate to severe renal dysfunction. Albeit, in Figure 1, it clear that there is increased toxicity at the extremes of renal function.

The authors highlight the lack of a consistent formula that accurately estimates GFR in cancer patients, particularly in the context of the relatively recent changes in the creatinine assay. However, the analysis focused on the Cockcroft-Gault estimation of GFR, which while acceptable by regulatory agencies during drug development has been shown to be inherently flawed.⁷ It is also likely that the recent changes in the creatinine assay, which began in 2005 (see <http://www.captodayonline.com/Archives/>

[0310/0310c_standardized_eGFR.html](#)) account for some of the apparent recent increase in GFR, as the IDMS-traceable creatinine assay has a lower normal range, and thus a higher “normal” range of calculated GFR.⁸ The same analysis conducted for comparing the toxicity across estimated GFR should have been performed for all of the renal function formulas. In addition, it would be helpful to better understand the independent effects of age and renal impairment, especially since the elderly are predisposed to toxicity for reasons other than decreased drug clearance.⁹ This would have aided in determining which formulas may be most useful to predict toxicity, which was the main concern. Indeed, the majority of the agents assessed (Table S1) had clinical trials conducted in the era of BSA-based dosing highlighting the importance of defining renal impairment with normalization to BSA.¹⁰ Without such normalization, patients with decreased Cockcroft-Gault calculated GFR may simply be smaller or older.

The primary conclusions drawn from this retrospective analysis are accurate and demonstrate the lack of increased toxicity in patients with mild renal impairment. This obviates the need for a dedicated mild renal impairment cohort during the conduct of a trial unless the moderate or severe cohorts point to major discrepancies in tolerability and pharmacokinetics. The analysis by Beumer and colleagues also points to the need for harmonization of estimations of renal function during drug development to provide clear guidance on dosing. Our recommendation would be to utilize one standardized formula in the IDMS-traceable creatinine era with normalization to BSA, when appropriate. In addition, there should be greater emphasis on the independent effects of aging and renal injury, to avoid attribution of pharmacokinetic and pharmacodynamic effects of aging to decreased renal function. Continued assessments of how renal function impacts dose optimization in oncology drug development is needed and may involve integrated approaches which consider the totality of relevant information, including clinical pharmacology data and population pharmacokinetic analyses.

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