Evaluation of NMR-Based GFR Estimation in High-Dose Methotrexate Administration

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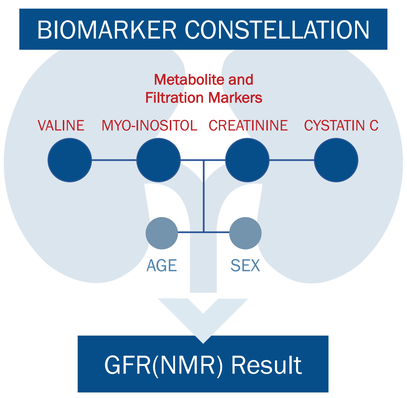
BACKGROUND

The cytotoxic agent methotrexate (MTX) is used primarily in oncology and rheumatology and is 80%-90% excreted unchanged in the urine. The impaired renal excretion found in kidney disease leads to MTX accumulation and prolonged exposure, increasing risk of myelosuppression and other adverse effects. Direct kidney damage from MTX crystal precipitation and tubular injury may also occur.

Figure 1. GFR(NMR) Constellation

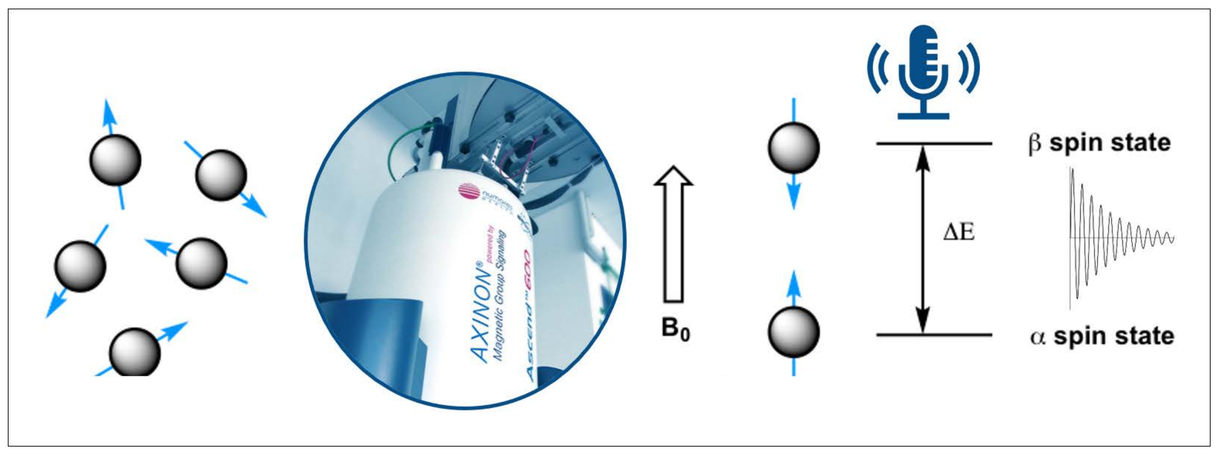


Therefore, precise and accurate renal function measurement before MTX administration is critical in determining accurate dosing, minimizing the risk of adverse effects. Commonly used estimated glomerular filtration rate (eGFR) equations perform poorly in patients with cachexia and advanced age, including many oncology patients. Here we evaluate the feasibility of applying the recently introduced nuclear magnetic resonance (NMR)-based GFR equation, GFR_{NMR}, using creatinine, cystatin C, myo-inositol and valine (Fig. 1), in oncology patients receiving high-dose MTX.

METHODS

A series of residual sera from patients scheduled to receive high-dose MTX infusion for oncologic indications were collected from two sites: n=52 sera from University Hospital Regensburg (Regensburg, Germany), at four times (t0h, t24h, t42h and t48h); and n=10 cross-sectionally from Mayo Clinic (Rochester, Minnesota). Standard drug-monitoring trough levels were used as a reference. Serum was prepared and NMR-measured (Fig. 2) in five replicates for all samples. GFR_{NMR} was compared with the current standard GFR equations: CKD-EPI_{2021}Cr (creatinine) and CKD-EPI_{2021}CrCys (creatinine and cystatin C). Coefficient of determination for linear regression, kappa coefficient for categorical regression and bootstrapped confidence intervals were calculated.

Figure 2. Nuclear Magnetic Resonance (NMR) Spectroscopy



RESULTS

MTX was shown not to increase the GFR_{NMR} failure rate or affect its intra-assay precision, (Fig. 2). When monitoring eGFR during high-dose MTX treatment, MTX affected GFR according to the RIFLE criteria for AKI in 13 cycles in 9 patients (Fig. 3); 1/13 were classified as 'risk' (creatinine increased 1.5-fold) and 1/13 were classified as 'injury' (creatinine increased 2.0-fold). Using MTX clearance as a surrogate for measured GFR (Fig. 4), GFR_{NMR} reflected the MTX plasma clearance constant k more accurately (using a fitting function $c=c_0*e^{-kt}$) with r=0.758 (95% CI 0.36-0.92, p=0.004), compared to CKD-EPI_{2021}Cr (r=0.401, 95%CI -0.19-0.78, p=0.176) and CKD-EPI_{2021}CrCyc (r=0.632, 95% CI 0.12-0.88, p=0.023).

Figure 3. GFR(NMR) Repeatability Coefficient of Variation

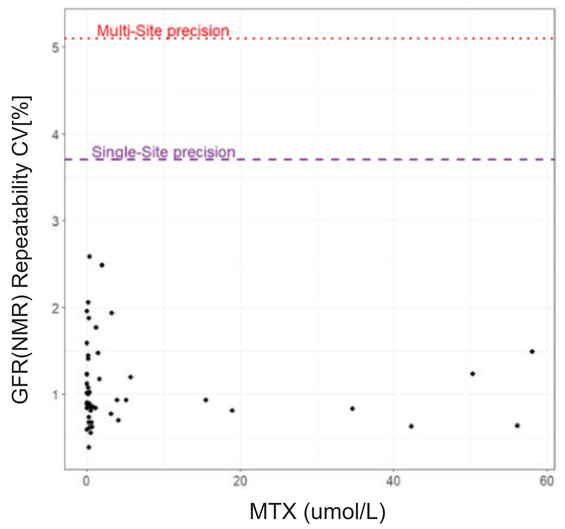
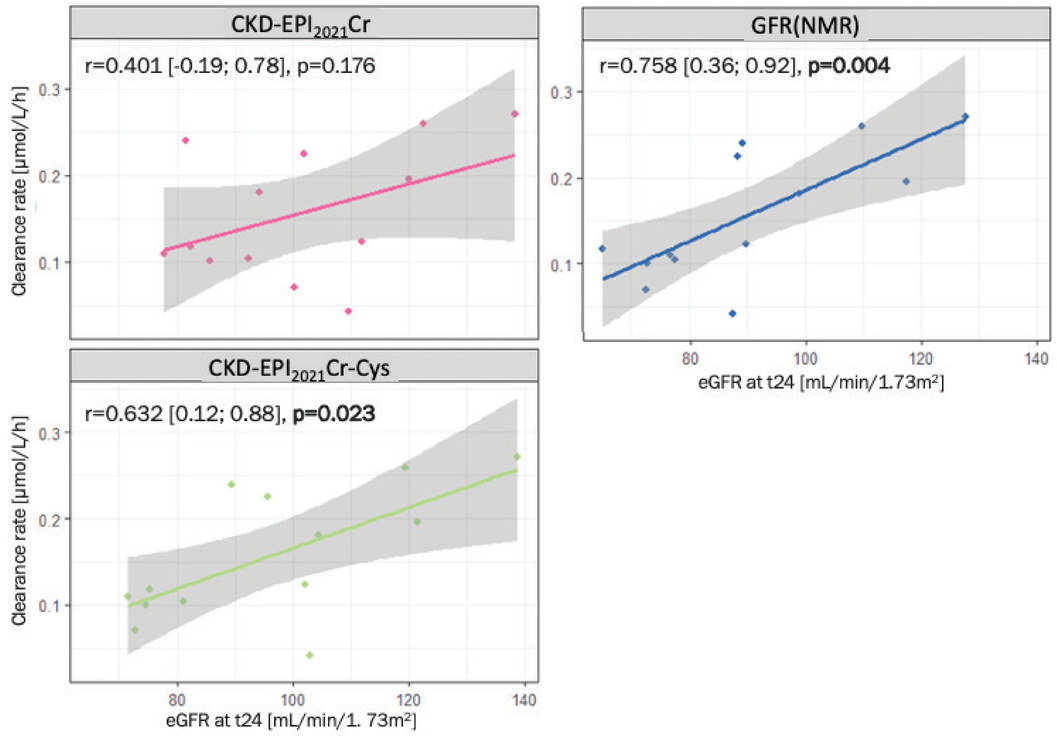


Figure 4. MTX Plasma Clearance by GFR Equations



CONCLUSION

The robustness of the GFR_{NMR} results is not affected by high-dose MTX treatment. Compared to standard eGFR equations, GFR_{NMR} is more closely associated with MTX renal clearance rates and may therefore be a novel method to improve MTX dosing accuracy in the future.

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