NMR-Based Biomarker Measurement Determines High-Dose Methotrexate Elimination Rates in Lymphoma and Leukemia Treatment

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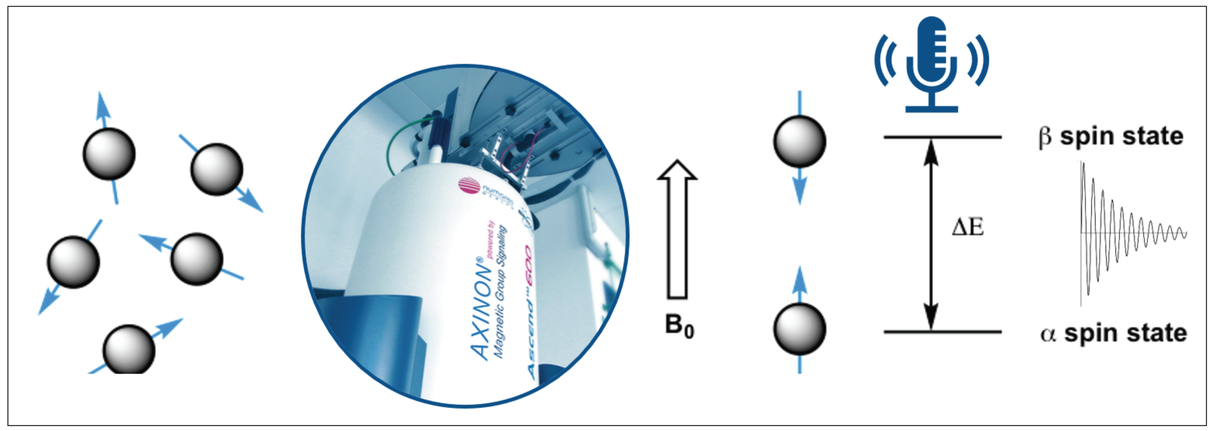
BACKGROUND

The cytotoxic methotrexate (MTX) is used in high doses in central nervous system (CNS) lymphoma, a rare subtype of non-Hodgkin's lymphoma, and acute lymphocytic leukemia (ALL) treatment. A therapeutic plasma dose range is crucial to minimize MTX accumulation and prolonged exposure, which can lead to myelosuppression, nephrotoxicity and other adverse effects.

Figure 1. Nuclear Magnetic Resonance (NMR) Spectroscopy



Determining MTX elimination before drug application is difficult, given its non-linear clearance, which uses both simple glomerular filtration and active tubular secretion. Here we present a model to predict MTX elimination rate in patients receiving high-dose methotrexate, based on metabolite measurement using nuclear-magnetic resonance (NMR) spectroscopy (Fig. 1).

METHODS

For a series of n=26 MTX infusions as per treatment protocols for CNS lymphoma (MATRIX protocol, 3.5 g/m² over four hours) or n=16 ALL (GMALL protocol, 1.5 g/m² over 24 hours), residual sera were collected at the University Hospital Regensburg at four timepoints (t0, t24, t42 and t48). Serum was NMR-measured in five replicates. NMR spectra for each sample were characterized and relevant parameters extracted. First order elimination constants were modeled for two MTX dosage regimes (<4 g, ≥4 g) using characterized NMR features from samples measured at t0, using first order c(t)~c0*e(-kt) kinetic function.

RESULTS

Metabolomic and lipidomic biomarkers measured at baseline (t0) were able to accurately predict MTX elimination rate constant k, determined by fitting MTX levels at a t24, t42 and t48, (panel A: ≥4 g: $R^2 = 0.48$, p-value < 0.05 (Fig. 2); panel B: <4 g: $R^2 = 0.92$, p-value < 0.001) (Fig. 3). Results were cross-validated with five-time repeated three-fold cross-validation. Performance values are given as means of the folds.

Figure 2. Panel A, predicted MTX elimination in ALL patients

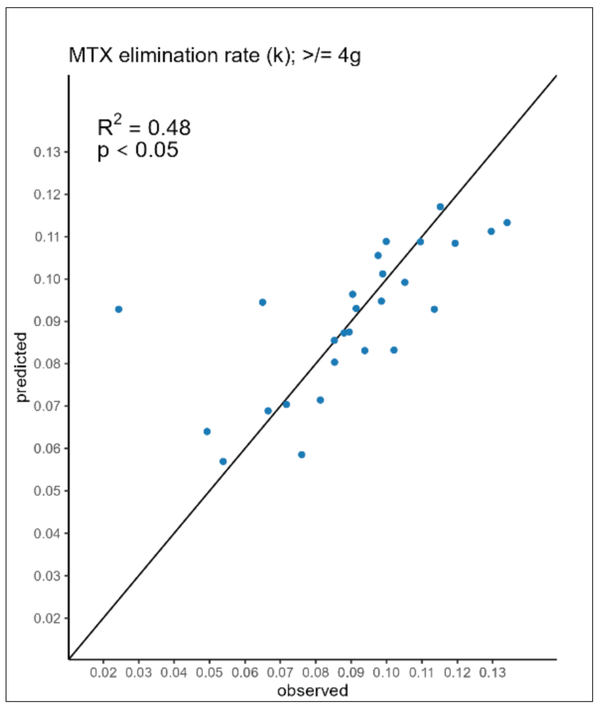
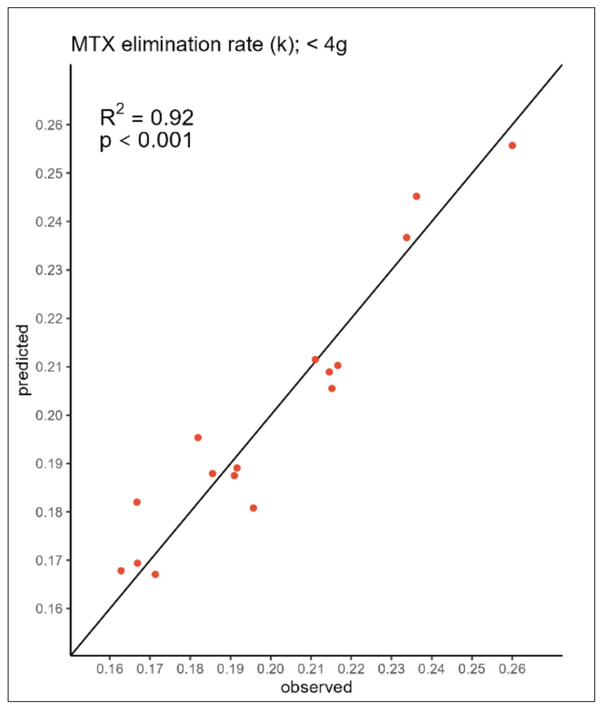


Figure 3. Panel B, predicted MTX elimination in CNS lyphoma patients



CONCLUSION

NMR-measured biomarkers can predict dose-dependent MTX elimination rates in patients receiving high-dose MTX for CNS lymphoma and ALL. These results present a novel method to predict MTX clearance, which potentially can allow for personalized dose-monitoring and minimization of adverse events. Future validation studies with a larger cohort is warranted.

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