Intra-Tumor Pharmacokinetics of Methotrexate in Mice Using Microdialysis

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ABSTRACT

This work is aimed to investigate methotrexate (MTX) disposition at tumor-site using microdialysis in a tumor-bearing mouse model. The plasma concentration-time profiles were obtained from normal mice, while microdialysis technique was employed to characterize the time course of MTX concentrations in the tumor core. Disposition profiles of plasma and tumor were analyzed by two modeling approaches: (a) compartmental and (b) hybrid physiologically-based pharmacokinetic (hPBPK) models using SAAM-II software. While previous attempts to build compartmental models were solely relied on MTX plasma concentrations, in the current study MTX concentrations were available from both plasma and tumor sites. Therefore, an incorporation of tumor MTX data in the compartment model allowed for a better quantitative description of the disposition of MTX. In the compartmental model, plasma and tumor concentrations were simultaneously fitted to obtain rate constants of plasma-tumor transport. However, because the compartment model has minimum physiological significance, an hPBPK model was developed to incorporate more physiologically-relevant parameters, such as tumor blood flow and tumor interstitial volume into the model. The hPBPK model was focused more on MTX disposition in the tumor and allowed for the prediction of different scenarios upon a perturbation of PK parameters of the model using the sensitivity analysis. Both mechanism-based compartmental and hybrid PBPK models were able to accurately define the atypical transport of MTX in the tumor, providing a pharmacokinetic basis for characterizing the tumor distribution of drugs guided by microdialysis techniques. This information can ultimately aid in the development of anticancer drugs with improved PK profiles.

BACKGROUND

MTX is a commonly used chemotherapeutic agent in the treatment of variety of human cancers.
MTX inhibits cell growth by blocking dihydrofolate reductase activity.
MTX effect on tumor depends on its levels at target site in tumor tissues. However, only “plasma” concentration-time profile is determined in cancer patients.
Microdialysis allows for direct measurement of MTX levels in tumor using animal models.
Pharmacokinetic modeling provides a predictive tool that can correlate the plasma concentrations with tumor concentrations of the therapeutic agents.

OBJECTIVE

To develop pharmacokinetics models that will help to predict MTX tumor concentration-time profile from plasma concentrations.

METHODS

To enhance accuracy of the model, MTX time-concentration profiles from both plasma and tumor were used.
Plasma concentrations were obtained over time after iv bolus injection of MTX and were converted into free plasma concentrations of MTX.
Tumor concentrations were determined in microdialysate from tumor tissue.
Both time-concentration profiles were analyzed by two pharmacokinetic modeling approaches:
(a) Compartmental model
(b) Hybrid Physiologically-Based Pharmacokinetic (hPBPK) model

RESULTS

A) Compartmental Model:

B) Hybrid Physiologically-Based Pharmacokinetic (hPBPK) Model:

CONCLUSIONS

Two pharmacokinetics models were developed to describe MTX disposition in tumor tissue.
The PK models indicate that tumor MTX concentration is influenced by the efflux of MTX from the tumor interstitial zone.
Both compartmental and hybrid (hPBPK) models support the idea that MTX undergoes diffusion-limited transport in tumor.

References: