248d Pharmacokinetic Analysis of Motexafin Gadolinium in Mouse Tissues Using a Non-Invasive Optical Measurement System

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In order to optimize the effect of the anti-cancer drug Motexafin Gadolinium (MGd), tissue-specific drug concentration information is required. Studies have considered MGd for use in combination with other chemotherapeutics and/or radiation therapy [3], where MGd facilitates the generation of reactive oxygen species which lead to apoptosis. A key consideration in radiation therapy is the elapsed time between MGd administration and tumor irradiation, since effective treatment is associated with a preferential MGd concentration gradient between tumor (high) and normal tissue (low). Current methods for measurement of *in vivo* drug concentration involve either destructive tissue analysis or magnetic resonance imaging, neither of which is currently applicable to a real-time clinical treatment regimen.

A novel method for *in vivo* drug quantitation is the optical pharmacokinetic system (OPS), a fiber-optic based spectroscopy system. The OPS measures elastic-scattering of light at an accesible tissue site, with changes in absorbance (or transmittance) due to changes in drug concentration calculated by Beer's Law [1]. Absorbtion changes are quantitated by the following metrics: (1) integrated area under the absorbtion profile between specified wavelengths (*e.g.*, 650-810 nm); or (2) the height of peak absorbance at a specified wavelength (*e.g.*, maximum absorbance). An algorithm was developed to compute these metrics from measured intensity spectra of a sample (medium with drug) and the respective baseline (medium with no drug). Standard curves are used to relate the metric magnitude to MGd concentration. The standard curves are constructed *in vitro* (in well-plates) and used to estimate MGd concentrations *in vivo*.

OPS measurements are compared with standard destructive tissue analysis using high preformance liquid chromotography (HPLC), the standard method of quantitating MGd concentrations in mouse tissues [2]. Mice bearing subcutanously implanted MDA-MB-231 xenografts were administered MGd, and OPS measurements were made at specific times after dosing on selected tissues pre- and post-exsanguination. Analysis of PK data shows that the OPS detects MGd *in vivo* with absorbtion bands separate from dominant endogenous materials (*e.g.*, hemoglobin). Sensitivity of OPS-measured *in vivo* MGd concentrations to changes in standard curve experimental parameters (*e.g.*, fluid volume depth) are investigated. Concentration vs. time profiles were generated (per tissue) via both OPS and HPLC, and were used to develop compartmental pharmacokinetic (PK) models.

A key issue is the discrepancy noted between MGd concentrations measured by OPS and HPLC for some tissues. OPS measures on *in vivo* tumors (measurement of the subcutaneous tumor by light penetration through the skin) do not show MGd accumulation or retention detected by HPLC. Moreover, OPS measures on *in vivo* tumors were similar to *in vivo* skin, with both measures following a similar qualitative time-course to plasma. These results question whether the light penetration depth is adequate enough to interrogate tumor tissue. We investigate the factors contributing to OPS measured MGd concentrations in tumors *in vivo*, including MGd contained in skin and plasma. Using the tissue-specific PK descriptions of MGd in skin and tumor tissue (with and without plasma) we estimate explicit tumor tissue MGd concentrations from *in vivo* OPS measures on tumors.

Bibliography

1 J. R. Mourant, T. M. Johnson, G. Los, and I. J. Bibio. Non-invasive measurement of chemotherapy drug concentrations of *in vivo* measurements. *Phys Med Biol*, 44:1397-1417, 1999.

2 R. A. Parise, D. R. Miles, and M. J. Egorin. Sensitive high-preformance liquid chromatographic assay for motexafin gadolinium and motexafin lutetium in human plasma. *J Chromatogr B Biomed Sci Appl*, 749(2):145-52, 2000.

3 D. I. Rosenthal, P. Nurenberg, C. R. Becerra, E. P. Frenkel, D. P. Carbone, B. L. Lum, R. Miller, J. Engel, S. Young, D. Miles, and M. F. Renschler. A phase I single-dose trial of gadolinium texaphyrin (Gd-Tex), a tumor selective radiation sensitizer detectable by magnetic resonance imaging. *Clin Cancer Res*, 5(4):739-45, Apr 1999.