Imaging Biomarkers of Treatment Response: Applications to Clinical Trials

Peter Scully

Under the supervision of Robert Jeraj

At the University of Wisconsin-Madison

2015

Quantitative imaging biomarkers - numerical measurements derived from medical imaging that can be interpreted by clinicians - are a critical component of treatment response assessment in oncology. They can also play an important role in the design and interpretation of clinical trials, provided that they are measured following a standardized set of best practices. In this thesis, we have demonstrated the successful application of imaging biomarkers of treatment response to a clinical trial assessing the pharmacodynamics and pharmacokinetics of the anti-angiogenic TKI therapeutic Axitinib. We have illustrated the challenges facing quantitative imaging biomarkers in general, and gained valuable insights into anti-angiogenic therapy in particular.

We have characterized the pharmacodynamics of "withdrawal flare," a rapid increase in tumor proliferation following cessation of anti-angiogenic therapy, using quantitative imaging biomarkers derived from FLT PET. This is the first time in humans that the temporal dynamics of Axitinib withdrawal flare have been characterized, a critical step in optimizing the use of this drug in combination therapy. Although we demonstrated that significant flare occurs in patients treated with Axitinib, we also observed substantial inter-patient heterogeneity in imaging response during withdrawal. Among the sub-set of patients experiencing withdrawal flare, it was found to occur at two days post-cessation of Axitinib, with relatively little additional flare between days 2 and 7 of withdrawal. Moreover, withdrawal flare was found to be associated with poor clinical outcome.

We directly compared the results of the Axitinib trial with an earlier trial of a related anti-angiogenic drug, Sunitinib, which had used the same imaging biomarkers of treatment response. The proliferative and vascular response during withdrawal of Axitinib and Sunitinib was found to be nearly identical, and there is not sufficient evidence to support any significant difference in proliferative response during treatment. We also explored intra-patient, inter-lesion response heterogeneity. However, when comparing the imaging response with pre-treatment phenotypes, no significant correlations were observed, suggesting that some underlying biological mechanisms may be driving the inter-lesion differences in response.

The insights gained from this original work support several hypotheses for how to improve patient treatment. These hypotheses will be partially addressed in three new ongoing clinical trials at the University of Wisconsin.