An adaptive, patient-specific treatment approach for EGFR-driven, stage IV lung cancer

Jill Gallaher[1], Olya Grove[1], Daniel Nichol[2], Hildur Knútsdóttir[3], Joshua Scurll[3], Lori Hazelhurst[1], Ben Creelan[1] and Philip Gerlee[1]

Acquired resistance to targeted cancer drugs is an unfortunate but inevitable consequence of the evolutionary dynamics of cell clones in a malignant tumor. At the Third Integrated Mathematical Oncology (IMO) Workshop at the Moffitt Cancer Center[1], the theme of which was *Personalized Medicine*, we proposed a model for a new approach to treating stage IV non-small cell lung cancer (NSCLC) patients whose cancer is driven by a mutation in the gene encoding epidermal growth factor receptor (EGFR). This new approach is both adaptive and personalized, and aims to, as far as possible, overcome the effects of acquired resistance.

LUNG cancer is the leading cause of cancer-related mortality in North America [1]. It can typically be classified at the molecular level by oncogene mutations that drive the cancer, with one such mutation occurring in the EGFR oncogene. Standard of care for patients suffering from stage IV (metastatic) non-small cell lung cancer (NSCLC) that is being driven by an EGFR oncogene mutation is to give the patient an EGFR tyrosine kinase inhibitor (TKI) such as erlotinib, but unfortunately most patients develop acquired resistance to the drug within a year or so, and survival rates are poor, with median survival time less than two years.

I will present a $50,000-grant-winning model aimed at tackling this problem, which I developed as part of a team at the Integrated Mathematical Oncology (IMO) Workshop on Personalized Medicine at the Moffitt Cancer Center, Tampa, Florida in November 2013. We first simplified the EGFR pathway down to five key genes and subsequently developed a model that describes the evolutionary dynamics of the number of cell clones harboring various combinations of gene mutations or amplifications. Using a threshold tumor burden as an indicator of patient death, we proceeded to use a genetic algorithm to predict a locally optimal sequence of drug combination therapies to maximize patients' survival times. When simulated on a cohort of 100 virtual patients, our model's selected treatment schedule predicted a prolongation of survival by an average of 45 days compared with standard of care erlotinib. Moreover, our model allows for new patient data to be fed back into the model every time new data (e.g. imaging) is available from a patient, thus allowing the model to be continually refined and increasingly personalized for individual patients.

Acknowledgements: This work took place at the Third Integrated Mathematical Oncology Workshop at the Moffitt Cancer Center[1].

[1]Moffitt Cancer Center, Tampa, FL, USA
[2]Department of Computer Science, University of Oxford, UK
[3]Department of Mathematics, University of British Columbia, Vancouver, BC, Canada

REFERENCES

[1] National Cancer Institute: *Surveillance, Epidemiology and End Results Program*, Cancer Statistics, http://seer.cancer.gov/statfacts/ (correct as of 14 April 2014).