IN SILICO INVESTIGATION OF ANTI-ANGIOGENIC AND CYTOTOXIC TREATMENTS ON AN IN VIVO MAMMARY CARCINOMA MURINE MODEL

Myrianthi Hadjicharalambous (1), Vasileios Vavourakis (1,2)

1. University of Cyprus, Cyprus; 2. University College London, United Kingdom

Introduction

Chemotherapy, either conventional or metronomic, targeted or adjuvant, is one of the major treatment modalities against cancer, with continuous efforts focusing to improve its efficacy. For instance, chemotherapy has been considered in combinatory protocols with anti-angiogenic (AA) drugs. AA treatments have shown significant potential in preclinical trials, through their direct effects – blocking new vessels and reducing the density of the existing vasculature. Moreover, in a process termed vascular normalization, AA drugs can improve blood perfusion and thus enhance the chemotherapeutic efficiency, by changing vessels' pore and lumen size and by reducing interstitial fluid flow. Despite their promising potential, an improved understanding of AA drugs is necessary to enable their optimized administration.

In this contribution, we present an *in silico* multiscale cancer modelling framework, used to systematically investigate the role of individual mechanisms of action of AA drugs in tumour progression, with AA drugs considered as a monotherapy or in combination with chemotherapy.

Methods

The *in silico* modelling framework of cancerous growth spans across multiple scales by encompassing tissue and tumour biomechanics, angiogenesis, and blood flow through the vasculature and the interstitium [1,2]. It employs a partitioned finite element discretization approach to simulate the transport and balance of biochemical cues and the interaction among different cell populations (cancerous and healthy ones), and the delivery of cytotoxic agents. The model was used to interrogate several mechanisms of action of AA drugs and cytostatics. Initially, the importance of reducing the density of the existing vasculature was investigated, by employing four discrete vascular representations, corresponding to different levels of AA treatment. The vessels' pore size and diameter were modified, to elucidate the effect of vascular normalisation. The main mechanisms of AA agents were considered with AA as a monotherapy or in combination with conventional and metronomic chemotherapy.

Results

The *in silico* framework was employed to simulate solid tumour development and was specified to *in vivo* data from a mammary carcinoma xenograft in immunodeficient mice. Computer simulations revealed that the higher the dose of AA drug which disrupts the vasculature, the more profound the effect on tumour volume regression (Fig. 1), with even a medium dose causing an 80% reduction in tumour volume. However, a very high dose of AA drugs caused severe damage on healthy cells too.

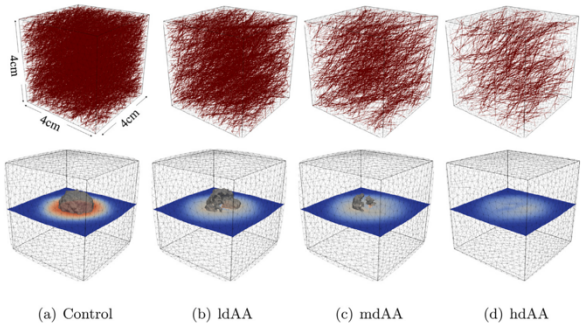

Figure 1: (Top) Vascular network for the (a) control simulation, or corresponding to a (b) low, (c) medium, and (d) high dose of AA therapy respectively. (Bottom) Effect of AA drugs on tumour volume shown as grey outline.

When combined with chemotherapeutics, a lower dose of AA drugs was able to shrink the tumour without causing such severe effects on healthy cells. Additionally, when chemotherapy was combined with vascular normalisation the effect on tumour regression was more pronounced (the final tumour volume is reduced from ~0.9 cm^3 (chemotherapy) to ~0.1 cm^3 (chemotherapy and vascular normalisation). Notably, metronomic chemotherapy demonstrated significant potential suppressing tumour growth with minimal toxicity to native tissue.

Discussion

Focusing on both the influence on tumour growth, tumour vasculature, and healthy tissue, our results indicated that combinatory treatments might be more beneficial than conventional chemotherapy alone [3]. Metronomic chemotherapy as a monotherapy can inhibit tumour growth with minimal toxicity, providing hope for a highly effective and well-tolerated therapy. Our findings underpin the potential of our *in silico* framework for non-invasive evaluation of therapeutic strategies for cancer regression and anti-angiogenic treatments.

References

1. Vavourakis et al, PLoS Comput. Biol, 14: 2018.
2. Wijeratne & Vavourakis, RS Interface Focus, 9: 2019.
3. Hadjicharalambous et al, J Theo Biol, 553: 2022.

Acknowledgements

The authors acknowledge funding from the European Regional Development Fund and the Republic of Cyprus (RESTART 2016-2020 Programme; ID: OPPORTUNITY/0916/MSCA/0012), and the Cyprus Cancer Research Institute (Bridges in Research Excellence CCRI_2020_FUN_001; ID: CCRI_2021_FA_LE_105).