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Effects of tissue hydraulic permeability on intracerebral transport of interstitial fluid and nanoparticle-encapsulated drugs upon convection-enhanced delivery

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Introduction

Convection-enhanced delivery (CED) as an alternative to intravenous administration is developed to bypass the blood-brain barrier (BBB). Since anticancer drugs are directly infused into the brain tumour tissue, the local interstitial fluid flow plays a critical role in determining the delivery outcomes. Tissue hydraulic permeability stands for the resistance of tissue to the interstitial fluid flow. It could vary considerably depending on the tissue components and microstructure. However, its effects on the delivery outcome of CED is less clear.

Methods

In this study, a mathematical model is developed to predict the enhanced interstitial fluid flow and drug transport in the CED treatment. A 3-D realistic model of brain tumour is reconstructed from patient Magnetic Resonance images. The model covers the key intracerebral drug delivery processes, including the release dynamics from nanoparticles, transport in interstitium by convection and diffusion, drug binding with proteins, physical degradation and metabolic reaction, and cell uptake, etc. The performances of four drugs are studied, including doxorubicin, carmustine, temozolomide and paclitaxel. The delivery outcome is evaluated in terms of the tumour volume where the drug concentration is sufficient to kill 90% of tumour cells.

Results

Modelling results show that the CED infusion can effectively increase the interstitial fluid pressure in the region around the infusion site, and thereby prompt the transport of fluid and drugs from tumour tissue to blood flow. This fluid and drug loss to blood is less significant in the permeable tumour. Nanoparticle concentration in tumour is found to be less sensitive to tissue permeability. The concentration of released free drugs is low in permeable tumours. However, a better delivery can be achieved in these tumours since the distribution is relatively homogeneous. Paclitaxel shows the most effective cell killing; it is followed by doxorubicin, temozolomide and carmustine. Moreover, these drugs present a similar response to the changes in tissue hydraulic permeability.

Discussion

The released drugs would accumulate around the infusion site in the less-permeable tumours, leading to the drug concentration becoming significantly low in the tumour region that is far away from the infusion site. As a result, the tumour cell killing is only effective in a limited region where the infusion takes place. The effect of tissue hydraulic permeability highlights the importance of drug distribution patterns in determining delivery outcomes.

Conclusions

Tissue hydraulic permeability as an intrinsic property can influence the transport of both interstitial fluid and drugs in brain tumours. Results from this study can deepen the understanding of interplays between drugs and the intratumoural environment in chemotherapy.

References

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