A minimal PKPD model to evaluate synergic effects of combined non small cell lung cancer therapies

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Contact person

Clara Mihaela Ionescu

Organisation

Name of the organisation Ghent University (UGent)
Department Department of Electromechanical, Systems and Metal Engineering
Country Belgium
Geographical Area Flemish Region

SCOPE OF THE METHOD

The Method relates to	Human health
The Method is situated in	Regulatory use - Routine production, Translational - Applied Research
Type of method	In silico

DESCRIPTION

Method keywords

Antiangiogenic therapy
Immunotherapy
Radiotherapy
Variability
Synergy modelling
Anomalous diffusion
Fractal kinetics

Scientific area keywords

Mathematical modelling
Lung cancer
Mouse data
Multiple therapy

Method description

This is a mathematical compartmental formulation of dose-effect synergy modelling for multiple therapies in Non Small Cell Lung Cancer (NSCLC): antiangiogenic, immuno- and radiotherapy. The model formulates the dose-effect relationship in a unified context, with tumor proliferating rates and necrotic tissue volume progression as a function of therapy management profiles. The model accounts for inter- and intra-response variability by

using surface model response terms. Slow acting peripheral compartments such as fat and muscle for drug distribution are not modelled. This minimal PharmacoKinetic-PharmacoDynamic (PKPD) model is evaluated with reported data in mice from literature and demonstrates physiological value. Furthermore, the model can be used to study therapy management protocols and is an aiding tool in the clinical decision making process. Although developed with data from mice studies, the model is scalable to NSCLC patients.

Lab equipment

No

Method status

Published in peer reviewed journal

PROS, CONS & FUTURE POTENTIAL

Advantages

The proposed PKPD model is minimal and simple which provides a good overview of essential features necessary to be introduced, such as effect sites, isobole surface models of interaction, degree of synergy among drugs and patient response to treatment (i.e., drug resistance). The model is directly scalable to diagnosed/treated NSCLC patients.

Challenges

The toxicity and risk of Radiation Pneumonitis (RP) affecting the healthy tissue in proximity of tumor volume voxel during RT treatment are not included in this model. Tissues with heterogeneous density have non-homogeneous drug distribution, hence drug trapping occurs. This can be modelled in PK compartmental formulation by adding a memory term, able to characterize long tail dynamics of drug release. The challenge to accommodate this in our model is the multi-scale pathway.

Modifications

When available, the numerical values introduced in the model parameters were assumed from literature. However, several parameters were not available, so the study introduced variability to assess their effect. The results suggest this is a fairly sensible model to be further calibrated on experimental data.

Future & Other applications

Such a minimal PKPD model once calibrated for the patient at hand, hence addressing the personalised medicine concept, can be used for evaluating various combination therapies. The model is successfully used to predict RP incidence in NSCLC treated with SBRT in patients. In view of time, cost and patient-related risks associated with unique emergency situations (e.g., pandemic outbreak), their relevance in regulatory decision-making on dose modification becomes crucial.

REFERENCES, ASSOCIATED DOCUMENTS AND OTHER INFORMATION

References

Ionescu C. M., Ghita M., Copot D., Derom E. and Verellen D. A Minimal PKPD Interaction Model for Evaluating Synergy Effects of Combined NSCLC Therapies. J. Clin. Med. 2020, 9, 1832; doi:10.3390/jcm9061832

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