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Title of contribution

Multiscale NSCLC Tumor Heterogeneity Knowledge-Based Model predicts Tumor Growth under Gefitinib

Introduction

New high-throughput techniques, tumor micro-environment exploration and genetic tumor cell heterogeneity data from various biological studies (pre-clinical and clinical) have significantly increased the understanding of Non-small cell lung cancer (NSCLC) related biological regulatory processes. Specifically, certain epidermal growth factor receptor (EGFR) gene mutations are associated with better

response to Tyrosine Kinase Inhibitors (TKI). However, making a precise clinical prognosis is difficult since the type of EGFR gene mutation might lead to different treatment responses.

We therefore developed an *in silico* EGFR+ lung adenocarcinoma (LUAD) model to predict the effect of EGFR-related mutations on tumor size in advanced-stage adenocarcinoma patients (IIIb or higher), which is based on a mechanistic representation of tumor evolution, including response to the TKI Gefitinib. Tumor heterogeneity, age, gender, initial clinical stage, and smoking status are included in the model as covariates.

Methods

5-step *in silico* model development:

1. Model Building using a Knowledge and a Computational Model (CM): Pathophysiology of EGFR+LUAD was characterized with seven sub-models: mutational burden, EGFR downstream pathways, tumor growth and heterogeneity, Gefitinib PK/PD, treatment-induced resistance and clinical outcome. For each sub-model, relevant biological entities and their functional relationships were extracted from scientific papers and translated into ordinary differential equations (ODEs). The CM has 43 variables, 170 parameters and 18 to 83 ODEs reflecting intra-tumor heterogeneity.

2. Calibration with information from scientific literature: Spheroids, xenografts and clinical results were used for stepwise calibration.

3. Virtual populations (VPOP): VPOPs were generated for validation and benchmarking respectively, adapting baseline characteristics of a real population .

4. Validation against published data: A Virtual Population with same baseline characteristics was tested against patients[1] extracted from published data, that were neither used for building nor calibration.

5. Benchmarking: The model was benchmarked with a Bayesian model (Nagase *et al.* 2020)[2] using two metrics: (1) the coverage of experimental interquartile range (IQR) with simulated IQR (model precision) assesses how well the model reproduces the experimental data, (2) the coverage of simulated IQR with experimental IQR (model overlap) assesses agreement of the model with experimental variability.

Results

Our model computed *in silico* data similar to the Bayesian reference model without accessing the original data for calibration (*Figure 1B bottom*: experimental vs simulated, model precision of 68%, model overlap of 91%). The Bayesian reference model displayed a model precision of 72%, and a model overlap of 86%.

[1]Paz-Ares L, et al. *Ann Oncol.* 2017;28(2):270-277.
[2]Nagase M, et al. CPT Pharmacometrics Syst Pharmacol. 2020;9(3):143-152.
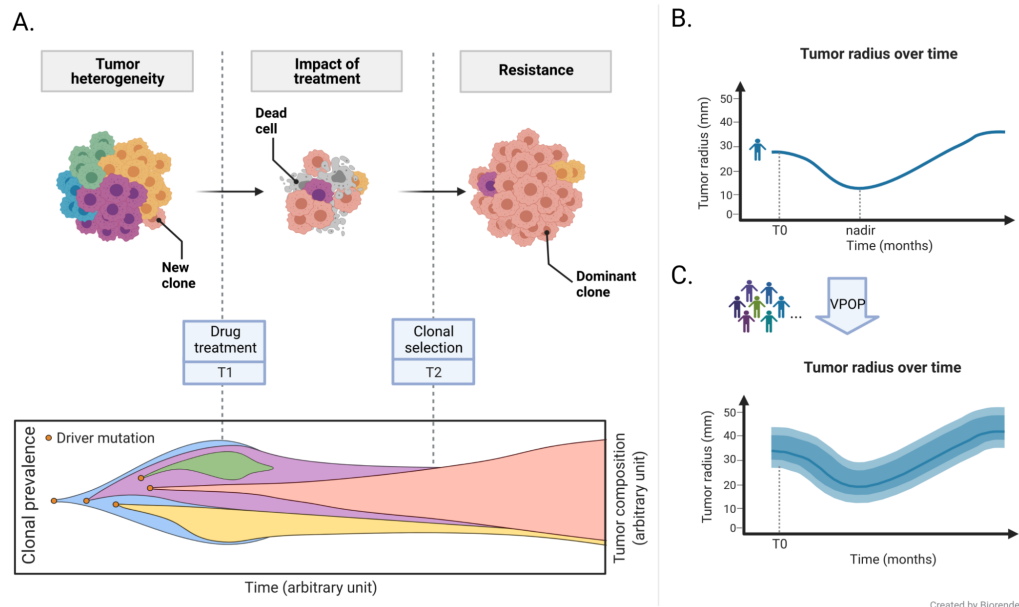
Figure 1: *Quantification of tumor progression over time measured by clonal prevalence and size.* Panel A: Illustration of tumor growth and heterogeneity. Panel B: Logarithmic tumor volume progression over time was computed (top figure) on the whole virtual population, and these *in silico* data (blue) were compared to the experimental logarithmic tumor volume (orange), assessed by median, first and third quartile as reported by Nagase et al. (bottom figure). [Precision = Common_IQR/Experimental_IQR ; Overlap = Common_IQR/Simulated_IQR]

Conclusion

We simulated tumor growth and treatment response in advanced-stage adenocarcinoma patients and validated successfully results statistically comparable to the study by Nagase *et al.* Access to patient-level data for calibration would have improved the precision of our model.