Modeling Tumor Dynamics and Overall Survival in Advanced Non–Small-Cell Lung Cancer Treated with Erlotinib

Ahmed Abbas Suleiman, MSc, Sebastian Frechen, MD,* Matthias Scheffler, MD,† Thomas Zander, MD,† Deniz Kahraman, MD,‡ Carsten Kobe, MD,‡ Jürgen Wolf, MD,† Lucia Nogova, MD,† and Uwe Fuhr, MD**

Introduction: Pharmacostatistical models can quantify different relationships and improve decision making in personalized medicine and drug development. Our objectives were to develop models describing non–small-cell lung cancer (NSCLC) dynamics during first-line treatment with erlotinib, and survival of the cohort.

Methods: Data from patients with advanced NSCLC (n = 39) treated first-line with erlotinib (150 mg/day) were analyzed using nonlinear mixed effects modeling. Exposure-driven disease-drug models were built to describe tumor metabolic and proliferative dynamics evaluated by positron emission tomography (PET) using 2′-deoxy-2′-[^{18}F]fluoro-D-glucose (FDG) and 3′-[^{18}F]fluoro-3′-deoxy-L-thymidine (FLT), respectively, at baseline, weeks 1 and 6 after starting erlotinib treatment. A parametric time-to-event model was built to describe overall survival (OS). Demographics, histology, mutational, smoking, and baseline performance statuses were tested for their effects on models developed, in addition to tumor dynamics on survival.

Results: An exponential relationship described progression, and a concentration-driven drug effect model described erlotinib effect. An activating epidermal growth factor receptor (EGFR) mutation increased the drug effect as assessed using FDG-PET by 2.19-fold (95% confidence interval [CI]:1.35–4.44). An exponential distribution described the times-to-death distribution. Baseline FDG uptake (p=0.0005; hazard ratio [HR] =1.26 for every unit increase, 95%CI: 1.13–1.42) and relative change in FDG uptake after 1 week of treatment (p=0.0073; HR=0.84 for every 10% drop, 95%CI: 0.71–0.91) were significant OS predictors irrespective of the EGFR mutational status. FLT-PET was statistically less significant than FDG-PET for OS prediction.

Conclusion: Models describing tumor dynamics and survival of advanced NSCLC patients first-treated with erlotinib were developed. The impacts of different covariates were quantified.

Key Words: Modeling, NSCLC, PET, Survival, Erlotinib.

(*J Thorac Oncol.* 2015;10: 84–92)

Lung cancer is the most commonly diagnosed cancer and the primary cause of cancer related mortality.[1] Non–small-cell lung cancer (NSCLC) accounts for approximately 85% of the lung cancer cases.[2] Despite the high medical needs, effective treatments available for advanced NSCLC are limited and the process of introducing new ones is inefficient.[3] Modeling and simulation have been endorsed among other tools to streamline drug development and therapy.[4–6] Nevertheless, a limited number of models have been developed for NSCLC.[7]

Pharmacostatistical NSCLC models have mostly used tumor size changes as an endpoint for response evaluation, or as a survival predictor.[8,9] However, evaluating the response of solid tumors to newer anticancer therapies using anatomical size-based assessments has been recently questioned since these therapies act by mechanisms unlikely to result in tumor shrinkage, and may prolong survival without tumor regression.[10,11] Therefore, evaluating the functional activity of tumors by positron emission tomography (PET) was recently promoted.[12] PET has demonstrated its usefulness in informing therapeutic decisions, and progressively took a crucial role in personalized cancer management. Similarly, using PET has a promising potential for decision making in anticancer drug development, an area where there is still a limited use of PET.[12] However, responses measured using PET are commonly categorized (progressive metabolic disease, stable metabolic disease, partial metabolic response, and complete metabolic response),[12,13] which can potentially discard information and reduce the statistical power of analysis similar to other categorical scales, and as a result the use of continuous scales was recommended.[14,15] Modeling offers a great opportunity to efficiently utilize continuous metrics either as endpoints or as covariates to investigate and quantify their effects on desired outcomes.

Several radionuclides have been used to evaluate the response of cancerous lesions to antineoplastic therapeutics using PET. 2′-deoxy-2′-[^{18}F]fluoro-D-glucose (FDG), a glucose analogue indicating the metabolic activity of the tissue,

*Department of Pharmacology, Clinical Pharmacology Unit, University Hospital of Cologne, Cologne, Germany; †Lung Cancer Group Cologne, Department I of Internal Medicine, Center for Integrated Oncology Cologne Bonn, University Hospital of Cologne, Cologne, Germany; and ‡Department of Nuclear Medicine, Center for Integrated Oncology Cologne Bonn, University Hospital of Cologne, Cologne, Germany.

Disclosure: None of the authors declared conflicting interests which are relevant to this manuscript or which can influence the judgments made in it. However, Jürgen Wolf has declared that a grant was received from Roche for the study, the data generated by which were used to develop the models presented in this analysis.

Address for correspondence: Ahmed Abbas Suleiman, MSc, Institute of Pharmacology, University Hospital of Cologne, Gleueler Str. 24, 50931 Cologne, Germany. E-mail: ahmed.suleiman@uk-koeln.de

DOI: 10.1097/JTO.0000000000000330

ISSN: 1556-0864/15/1001-0084

has been the most commonly used tracer.[16] 3′-[^{18}F]fluoro-3′-deoxy-L-thymidine (FLT), a thymidine nucleoside analogue giving a direct measure of the proliferative activity, has also been used.[17] A recent phase-II study by Zander et al.[18] evaluated and compared the accuracy of PET using FDG and FLT in early predicting nonprogression and survival in advanced NSCLC patients treated first-line with erlotinib, a tyrosine kinase inhibitor (TKI) acting on the epidermal growth factor receptor (EGFR). They found that an early metabolic response (≥30% reduction in FDG uptake) as measured using FDG-PET after 1 week of therapy was predictive of both nonprogression according to RECIST 1.0 (Response Evaluation Criteria in Solid Tumors)[19] after 6 weeks of therapy, and of overall survival (OS). An early response as measured by FLT-PET did not predict either.

Based on data from this trial, our first objective was to develop pharmacokinetic/pharmacodynamic models linking erlotinib exposure to the time courses of the dynamics of the tumors as assessed by FDG and FLT uptakes measured on a continuous scale in patients with advanced NSCLC treated first-line with erlotinib. Different covariate relationships which could affect the uptakes were evaluated and quantified. Second, we aimed to describe the times-to-death distribution of the cohort, and to evaluate different factors as OS predictors, among which are the tumor dynamics. Such models may possibly be used for simulations and informing decision making.[20]

PATIENTS AND METHODS

Patients, Data, and PET-imaging

Data were available from Zander et al.[18] (NCT00568841). Briefly, 40 patients with previously untreated stage-IV NSCLC were recruited for this phase-II study conducted at the University Hospital of Cologne, Germany. All patients gave written informed consents, and the study was approved by the local ethics committee and all other competent authorities. Patients were first-line treated with erlotinib at an oral dose of 150 mg once daily until progression or unacceptable toxicity. The dosage was reduced or suspended if a patient was intolerant to adverse reactions. Three FDG and FLT-PET scans were scheduled; (i) at baseline within 10 days before starting erlotinib (range of actual time relative to treatment initiation on which PET scans were made; FDG: -8 to 0 days; FLT: -9 to 0 days), (ii) 1 week (FDG: 6–12 days; FLT: 5–14 days), and (iii) 6 weeks (FDG: 41–53 days; FLT: 40–61 days) after starting therapy. The uptakes of FDG (101 observations) and FLT (99 observations), covariates, and OS data from 39 patients were used for analysis (one patient was excluded from analysis since he was irradiated within the first 6 weeks). Zander et al. excluded five more patients in their analysis; three patients died before any follow-up scans, and two patients had the treatment suspended for more than 2 weeks owing to toxicity. Patient characteristics are presented in Table 1.

FDG and FLT were synthesized as previously described.[21,22] An ECAT EXACT 47 scanner (Siemens, Erlangen, Germany) was used for obtaining PET images from the patients who had been fasting for at least 6 hours. Time intervals between tracer injection (doses on average, 365 ± 30 MBq of FDG and 305 ± 89 MBq of FLT) and image acquisition were 59 ± 14 (standard deviation) and 58 ± 15 minutes for FDG and FLT, respectively. Blood glucose measured before FDG-PET scanning was 123 ± 22 mg/dL. The attenuation-corrected scan trajectory covered 90 cm (6 bed positions: 5-min emission, 3-min transmission).

Scans were normalized to body mass, corrected for decay, dead time, scatter, and random coincidences, and reconstructed using ordered-subset expectation maximization. The same scanner, same acquisition protocol, and same reconstruction software were used for all patients on all visits. The standardized uptake value peak (SUV_{peak}) was estimated for each lesion using a 1.2-cm diameter fixed sized circle centered around the tumor area with the highest uptake. Five or fewer lesions having the highest SUVs (primary tumor or metastases) were selected and the SUV_{peak} of the hottest lesion at each time point, not necessarily the same lesion, served as the pharmacodynamic endpoint for model development.

Data Analysis, Software, and Model Selection Criteria

Nonlinear mixed effects modeling was used for analysis, and data were fitted to the models using NONMEM software (version 7.2).[23] The objective function value (OFV), a goodness-of-fit statistic computed by NONMEM, was used in discriminating between nested models (the lower the OFV, the better the fit). ΔOFV follows approximately a chi-squared distribution, and therefore a decrease of at least 3.84 points in the OFV for one degree of freedom was considered statistically significant ($p \leq 0.05$) for model discrimination. For covariate analyses, all covariate relationships were tested one at a time, and the relationship giving the biggest OFV drop was included in the model each step, provided that the drop was at least 3.84 points. This was repeated for the rest of the covariates until no significant drops in the OFV resulted.

Goodness-of-fit plots, bootstrap analyses, and visual predictive checks using R (versions 2.15.2 and higher),[24] Xpose4 (version 4.4.0),[25] Perl Speaks NONMEM (versions 3.5.3 and higher),[26] &/or Pirana (versions 2.8.2 and higher)[27] programs were used to assist model development.

Pharmacokinetic/Pharmacodynamic Model

Model development

No erlotinib concentrations were measured in the study, and therefore to drive the pharmacodynamic model, a published one-compartment pharmacokinetic model for erlotinib[28] was used to generate the individual pharmacokinetic parameters and plasma concentrations based on the individual set of covariates as identified by the pharmacokinetic model. It needs to be mentioned that α_1-acid glycoprotein (AAG) levels, identified among the significant covariates and found to result in approximately a 7.5% decrease in erlotinib clearance for every 10% increase in AAG levels, was not measured in the study. However, as AAG and erlotinib concentrations increase, the unbound fraction of erlotinib was expected not to change significantly, and only a modest effect on pharmacodynamics was speculated to result.[28]

