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ORIGINAL RESEARCH ARTICLE

Exposure–Response Analysis of Osimertinib in EGFR Mutation Positive Non-Small Cell Lung Cancer Patients in a Real-Life Setting

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Abstract

Background Osimertinib, an irreversible inhibitor of the epidermal growth factor receptor (EGFR) is an important drug in the treatment of EGFR-mutation positive non-small cell lung cancer (NSCLC). Clinical trials with osimertinib could not demonstrate an exposure-efficacy relationship, while a relationship between exposure and toxicity has been found. In this study, we report the exposure–response relationships of osimertinib in a real-life setting.

Methods A retrospective observational cohort study was performed, including patients receiving 40 - 80 mg osimertinib as ≥ 2 line therapy and from whom pharmacokinetic samples were collected during routine care. Trough plasma concentrations ($C_{min,pred}$) were estimated and used as a measure of osimertinib exposure. A previously defined exploratory pharmacokinetic threshold of 166 µg/L was taken to explore the exposure-efficacy relationship.

Results A total of 145 patients and 513 osimertinib plasma concentration samples were included. Median progression free survival (PFS) was 13.3 (95% confidence interval (CI):10.3 – 19.1) months and 9.3 (95% CI: 7.2 – 11.1) months for patients with $C_{min,pred} < 166$ µg/L and $C_{min,pred} \geq 166$ µg/L, respectively ($p = 0.03$). In the multivariate analysis, a $C_{min,pred} < 166$ µg/L resulted in a non-statistically significant hazard ratio of 1.10 (95% CI: 0.60 – 2.01; $p = 77$). Presence of a EGFR driver-mutation other than the exon 19 del or L858R mutations, led to a shorter PFS with a hazard ratio of 2.89 (95% CI: 1.18 – 7.08; $p = 0.02$). No relationship between exposure and toxicity was observed ($p = 0.91$).

Conclusion In our real-life cohort, no exposure–response relationship was observed for osimertinib in the current dosing scheme. The feasibility of a standard lower fixed dosing of osimertinib in clinical practice should be studied prospectively.

Keywords exposure–response analysis · NSCLC · osimertinib · pharmacokinetics-pharmacodynamics

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Introduction

Mutations in the epidermal growth factor receptor (EGFR) are frequently observed to be an oncogenic driver for the development of non-small cell lung cancer (NSCLC) [1, 2]. Several tyrosine kinase inhibitors targeting the intracellular domain of the receptor have shown to result in a significant improvement in progression free survival (PFS) and overall survival (OS) [2–4]. The development of secondary driver mutations, most commonly the T790M mutation, drove the development of the third generation EGFR-TKI of which osimertinib is currently approved by the EMA [5]. Osimertinib is mutant-selective TKI, having higher affinity for EGFR-mutant tyrosine kinase and less affinity for the wild type variant. Presently, based on the FLAURA trial, osimertinib is the preferred first line treatment option in patients with EGFR mutation positive (EGFRm +) NSCLC [6].

Osimertinib is dosed in a fixed oral dose of 80 mg once daily (QD) [5, 7]. It is reported that the between-subject variability in pharmacokinetic (PK) exposure of osimertinib is high, ranging from 20 – 78% in three combined clinical trial populations [7]. In these populations a broad range in baseline characteristics (weight, age, renal and hepatic function) were observed. Furthermore, the exposure of osimertinib was not associated with efficacy, nevertheless a relationship between exposure and the development of toxicity (such as rash, diarrhea and QTc prolongation) was observed [8]. In addition, it is becoming increasingly evident that sarcopenia is an important predictor for both drug exposure and treatment outcome [9, 10]. In general, patients in clinical practice tend to be more heterogeneous when compared to a standardized clinical trial population [11]. This urges confirmation of the observed treatment outcomes in a real-world setting, which has not yet been performed. Therefore, we set out to investigate the exposure-efficacy, exposure-toxicity and muscle mass-response relationships for patients receiving osimertinib in a real-life setting.

Materials and Methods

Ethics

The institutional review board authorized this study on July 19, 2019. The need for a written informed consent was waived as all data were collected as part of routine clinical care.

Patients

A retrospective observational study was performed. Between January 2016 and November 2019 patients receiving oral osimertinib treatment 40 or 80 mg QD in the Antoni van Leeuwenhoek Hospital (Amsterdam, The Netherlands) and of whom osimertinib plasma samples were drawn for routine care were included. Data on patient characteristics, including demographic characteristics (age, weight, height, smoking status and World Health Organization Performance Status (WHO PS)), prior treatment lines, tumor characteristics (primary EGFR mutation, tumor stage), osimertinib dose, treatment toxicity (toxicities described by the summary of product characteristics for osimertinib [5] and/or described by the prescriber to originate from the osimertinib intake) and PFS were retrospectively collected from patient records. At treatment initiation, radiological imaging was performed twice every six weeks, followed by every 12 weeks. Treatment was continued until progression.

Objectives

The primary objective of the study was to investigate whether the exposure to osimertinib in patients with NSCLC is related to efficacy. The secondary objectives were to study the relationship between osimertinib exposure and toxicity and the influence of (baseline) covariates on the efficacy of osimertinib. Covariates tested included gender, age, body mass index (BMI), WHO PS, neutrophil-to-lymphocyte ratio (NLR) at treatment initiation (± three weeks), primary EGFR driver mutation, smoking status (never (0 – 100 cigarettes)/ever (stopped > 100 cigarettes)/current (> 100 cigarettes) [12]), the number of previous lines of treatment, and sarcopenia. The endpoint for efficacy was defined as the PFS for osimertinib-treated patients. A predefined, exploratory pharmacokinetic threshold (based on the geometric mean reported by the Food and Drug Administration (FDA)) of 166 µg/L was used for the exposure-efficacy analyses [7, 13].

Calculation of Osimertinib Trough Concentrations

As routine measurement, osimertinib plasma samples were collected during patient visits to the outpatient clinic of the Antoni van Leeuwenhoek hospital. To calculate the time after osimertinib dose (TAD), the date and time of both the previous osimertinib intake and the blood sampling were recorded. Osimertinib plasma concentrations were determined using a validated liquid chromatography-tandem mass

spectrometry assay [14]. Predicted trough concentrations ($C_{min,pred}$) of osimertinib were approximated using the log-linear calculation using an earlier proposed algorithm [15]:

$$C_{min,pred} = C_{measured} * 0.5^{\frac{24-TAD}{t_{1/2}}}$$

where $C_{measured}$ is the measured plasma concentration of osimertinib and $t_{1/2}$ is the average elimination half-life of osimertinib (48 h [7]). Samples were excluded from the analysis if they were drawn: 1) before steady-state concentration of osimertinib was reached (240 h after start of osimertinib therapy), 2) with a TAD exceeding the half-life of osimertinib or 3) during osimertinib therapy beyond disease progression.

Exposure-Efficacy and –Toxicity Analysis

Efficacy of treatment in patients with a median $C_{min,pred} < 166$ µg/L was compared to efficacy in patients with a median $C_{min,pred}$ above this threshold. Patients who did not show progression prior to the final pharmacodynamic cut-off date, were censored. Covariates were included in the multivariable Cox regression analysis based upon their p-value in the univariable Cox regression analyses (covariates with a p-value < 0.1 were included). Toxicity analysis was performed by comparing the median $C_{min,pred}$ between patients with and without clinically relevant toxicities. These toxicities were defined as toxicities, which led to dose reductions, treatment interruptions or treatment discontinuations (at the discretion of the treating physician).

Measurement of Sarcopenia

Indices for skeletal muscle mass and sarcopenia were calculated based on computed tomography (CT)-scans of the third lumbar vertebrae (L3). Slice selection, segmentation and quantification of the adipose and muscle tissue was performed using Quantib Body Composition version 0.2.1 (Quantib BV, Rotterdam, the Netherlands) [16]. A threshold of > -15 Hounsfield units (HU) was set to exclude for intramuscular fat. Individual scans at baseline of therapy were reviewed on completeness and if necessary manually corrected. For diagnosing sarcopenia, the skeletal muscle mass index (SMI) was calculated as the sum of the delineated areas of the abdominal, psoas and erector spinae muscles divided by the squared height of the individual patient. Based on the findings of Martin *et al.* in patients with cancer, the following cut-off values for sarcopenia were used [17]:

- Males and BMI ≥ 25 kg/m^2: SMI < 53.0 cm^2/m^2
- Males and BMI < 25 kg/m^2: SMI < 43.0 cm^2/m^2
- Females: SMI < 41.0 cm^2/m^2

The influence of sarcopenia on the efficacy, toxicity and pharmacokinetics of osimertinib was examined.

Statistical Analysis

Statistical significant differences between the patient characteristics in both groups were assessed with a Chi-squared test, Fisher exact test or t-test when appropriate, a p-value < 0.05 was considered to be statistical significant. Statistical analyses were performed using R version 3.4.3 (R-project, Vienna, Austria). For the exposure-efficacy and the sarcopenia-efficacy relationship, univariate and multivariate analysis were performed using a Log-rank test. Additionally, univariate and multivariate Cox regression analysis were used to assess the effect of the individual covariates on the PFS. A cut-off p-value of 0.1 in the univariate analysis was used as inclusion criterion for the multivariate analysis. For the exposure-toxicity relationship a Wilcoxon signed rank test was used to assess a statistical significant difference in the median osimertinib $C_{min,pred}$ between patients with toxicities and those without toxicities.

Results

A total of 145 patients treated with oral osimertinib 40 or 80 mg QD between 2016 and 2019 were included. Table I provides an overview of the baseline characteristics. One patient received osimertinib 40 mg QD, all the other 144 patients received the standard dose of osimertinib 80 mg QD. A total of 513 osimertinib plasma concentrations were available, with a median of three samples per patient (range: 1–18 samples). The median trough concentration in the total patient population was 211 µg/L (range: 74.5 – 826 µg/L). Overall, 34 patients (23.4%) had a median $C_{min,pred} < 166$ µg/L. These patients were found to have a better performance status than patients with $C_{min,pred} \geq 166$ µg/L ($p = 0.034$). For a total of 66 patients (45.5%) NLR could not be calculated due to missing data. It was observed that patients with higher osimertinib exposure had a statistical significant increased NLR ($p = 0.020$). No other statistically significant differences were observed in the baseline characteristics of the included patients. An intrapatient pharmacokinetic variability of 20.8% and an interpatient variability of 37.5% were calculated for the standard dose of 80 mg osimertinib QD.

Exposure-Efficacy Analysis

On the final pharmacodynamic data cut-off date (September 1st, 2021) 21 patients were still on treatment with osimertinib, of which 14 patients were treated beyond progression. The median follow-up time was 21 months (range: 2.3

Table I Baseline Characteristics of the study population. BMI: body mass index; $C_{min,pred}$: predicted trough plasma concentration; EGFR: epidermal growth factor receptor; NLR: neutrophil-to-lymphocyte ratio; QD: once daily; WHO PS: World Health Organization performance status

	Median $C_{min,pred}$ < 166 ng/mL (n = 34)	Median $C_{min,pred}$ ≥ 166 ng/mL (n = 111)	*p*-value	Total (n = 145)
Gender, male	11 (32.4%)	26 (23.4%)	0.412	37 (25.5%)
Age at treatment initiation (years)	61 (31 – 88)	66 (42 – 86)	0.082	64 (31 – 88)
Primary EGFR mutation				
Exon 19 del	21 (61.8%)	61 (55.0%)	0.075	82 (56.6%)
Exon 19 del + other	0	2 (1.8%)		2 (1.4%)
Exon 21 L858R	11 (32.4%)	37 (33.3%)		48 (33.1%)
Exon 21 L858R + other	0	1 (0.9%)		1 (0.7%)
Other	0	10 (9.0%)		10 (6.9%)
Unknown	2 (5.9%)	0		2 (1.4%)
Smoking status				
Never smoked	17 (50.0%)	77 (69.4%)	0.066	94 (64.8%)
Current or former smoker	17 (50.0%)	33 (29.7%)		50 (34.5%)
Unknown		1 (0.9%)		1 (0.7%)
BMI (kg/m^2)	24.2 (19.8 – 40.5)	24.2 (17.9 – 37.3)	0.519	24.2 (17.9 – 40.5)
Tumor stage				
IIIa	3 (8.8%)	5 (4.5%)	0.595	8 (5.5%)
IIIb	1 (2.9%)	5 (4.5%)		6 (4.1%)
IV	30 (88.2%)	101 (91.0%)		131 (90.3%)
Central nervous system metastasis at osimertinib treatment initiation, yes	7 (20.6%)	38 (34.2%)	0.242	45 (31.0%)
Previous lines of therapy				
1	18 (52.9%)	55 (49.5%)	0.706	73 (50.3%)
> 1	16 (47.1%)	56 (50.5%)		72 (49.7%)
Osimertinib dose				
40 mg QD	0	1 (0.9%)	0.766	1 (0.7%)
80 mg QD	34 (100%)	110 (99.1%)		144 (99.3%)
WHO PS				
0	20 (58.8%)	45 (40.5%)	**0.034**	65 (44.8%)
1	14 (41.2%)	48 (43.2%)		62 (42.8%)
2	0	16 (14.4%)		16 (11.0%)
3	0	2 (1.8%)		2 (1.4%)
NLR	2.52 (1.24 – 13.1)	4.79 (0.267 – 22.0)	**0.020**	4.40 (0.267 – 22.0)

Bold entries are defined as a *p*-value < 0.05

– 80 months), with a median treatment time of 16 months (range 1.4 – 80 months). Progression occurred in 135 (93.1%) patients with a median PFS of 10.2 months (range: 1.3 - 64.6 months). In total, 31 patients (91.2%) in the cohort with a $C_{min,pred}$ < 166 µg/L and 104 patients (93.7%) in the cohort with a median $C_{min,pred}$ ≥ 166 µg/L were found to have progressed during osimertinib therapy. The Kaplan–Meier curve for the PFS is depicted in Fig. 1. The median PFS in the $C_{min,pred}$ < 166 µg/L was 13.3 months (95% CI: 10.3 – 19.1 months), while a median PFS of 9.3 months (95%CI: 7.2 – 11.1 months) was observed for the $C_{min,pred}$ ≥ 166 µg/L (p = 0.03). Table II and III show the univariable and multivariable Cox regression analysis on the PFS, respectively. The presence of brain metastases prior to osimertinib therapy, the primary EGFR mutation and the number of previous lines of treatment were found to result in a statistically significant higher hazard ratio. In the multivariable analysis, a $C_{min,pred}$ ≥ 166 µg/L was not statistically significant associated with a lower PFS and a driver mutation other than the exon 19del and exon 21L858R and the presence of brain metastasis at treatment initiation are found to be of statistically significant influence on the PFS with a hazard ratio of 2.891 (95% CI: 1.180 – 7.082) and 1.777 (95% CI: 1.024 - 3.082), respectively.

Exposure-Toxicity Analysis

In total, 33 patients experienced a clinically relevant toxicity during osimertinib treatment. The development of these toxicities led to dose reductions (n = 25), treatment interruptions (n = 13) and/or treatment discontinuation (n = 4). Toxicities included gastrointestinal disorders (n = 12), skin disorders (n = 9), fatigue (n = 3), decrease in renal function (n = 4), muscle pain/weakness (n = 3), ocular toxicities (n = 3), pneumonitis (n = 2), increase in liver enzymes (ALAT/ASAT)

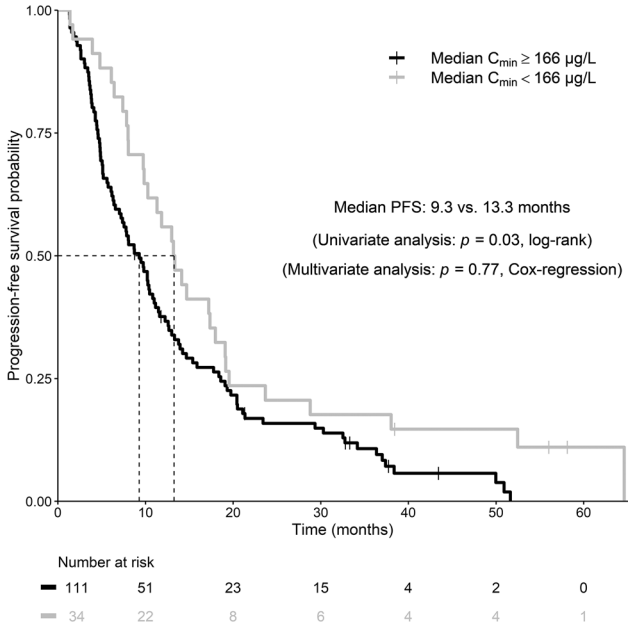

Fig. 1 Kaplan–Meier curve of PFS in patients treated with osimertinib in patients with median $C_{min,pred}$ below the population median of 166 µg/L (gray line) and in patients with a median osimertinib $C_{min,pred} \geq 166$ µg/L (black line). The dotted line represents the median PFS (in months). C_{min}: trough plasma concentration; PFS: progression free survival

(n = 2), cardiac toxicity (n = 2) and paronychia (n = 1). In 24 patients, these toxicities were observed after the collection of ≥ 1 PK sample. The median osimertinib $C_{min,pred}$ of these patients before the observation of these toxicities was 207 µg/L (range: 121 – 433 µg/L) compared to 213 µg/L (range: 96.9 – 826 µg/L) in patients who did not experience any clinically relevant toxicity ($p = 0.909$).

Measurement of Sarcopenia

Complete CT-scans including the L3 area were available for 122 (84.1%) patients. The median time between CT-scan and start of osimertinib therapy was 29.0 (±42.3) days. Sarcopenia was present in 93 patients (76.2%). In Fig. 2, the Kaplan–Meier curve in relation to the PFS in these patients is depicted. No statistically significant difference in PFS between patients with and without sarcopenia was observed (median PFS: 10.3 (95% CI: 8.7 – 13.0) months vs. 7.8 (95% CI: 4.9 – 14.2) months, resp. $p = 0.129$). Moreover, no relationship between the pharmacokinetics of osimertinib and the sarcopenia status ($p = 0.868$) was found. Regarding toxicity, patients who were rendered to have sarcopenia, were not prone to more clinically relevant toxicity compared to patients without sarcopenia ($p = 0.720$).

Discussion

In this retrospective cohort, we studied the influence of pharmacokinetic exposure of osimertinib on the response and toxicity of 145 patients treated with 40 or 80 mg osimertinib QD in daily clinical practice. We found that patients with a median osimertinib plasma $C_{min,pred} < 166$ µg/L had a numerically longer median PFS compared to patients with a $C_{min,pred} \geq 166$ µg/L (13.3 vs. 9.3 months, respectively). In the multivariate analysis, this trend was not observed to be statistically significant indicating that other well-known prognostic factor contribute to this difference. Moreover, exposure to osimertinib was not statistically significantly related to the development of clinically relevant toxicities. In addition, no statistical significant relationships between sarcopenia index and exposure or toxicities were observed.

Table II Univariable Cox regression analysis on progression free survival. BMI: body mass index; $C_{min,pred}$: predicted trough plasma concentration; EGFR: epidermal growth factor receptor; NLR: neutrophil-to-lymphocyte ratio; WHO PS: World Health Organization performance status

Variable	Hazard ratio	95% confidence interval	*p*-value
Gender, female	0.709	0.478 – 1.051	0.087
Age	0.995	0.981 – 1.010	0.501
Smoking status, never	0.854	0.598 – 1.221	0.387
BMI	0.984	0.939 – 1.032	0.508
Stage, IV	1.023	0.563 – 1.859	0.941
Brain metastases, yes	1.474	1.019 – 2.132	0.039
Primary EGFR mutation (relative to Exon 19del)			
Exon 21 L858R	1.292	0.892 – 1.870	0.176
Other	4.129	2.072 – 8.227	**0.00005**
Exon19 del + other	0.682	0.164 – 2.837	0.599
Exon 21 L858R + other	4.189	0.569 – 30.83	0.160
Unknown	0.281	0.039 – 2.057	0.212
WHO PS	1.185	0.937 – 1.501	0.157
NLR	1.040	0.994 – 1.089	0.091
No. of previous lines of treatment	1.180	1.025 – 1.358	**0.021**
Median osimertinib $C_{min,pred} < 166$ µg/L	0.629	0.414 – 0.955	**0.030**

Bold entries are defined as a *p*-value < 0.05

Table III Multivariable Cox regression analysis on progression free survival. $C_{min,pred}$: predicted trough plasma concentration; NLR: neutrophil-to-lymphocyte ratio

Variable	Hazard ratio	95% confidence interval	*p*-value
Gender, female	0.946	0.526 – 1.702	0.853
Mutation, other	2.891	1.180 – 7.082	**0.020**
NLR	0.996	0.943 – 1.051	0.870
Brain metastasis	1.777	1.024 – 3.082	**0.041**
No. of previous lines	1.112	0.849 – 1.476	0.425
Median osimertinib $C_{min,pred} < 166$ µg/L	1.097	0.599 – 2.007	0.765

Bold entries are defined as a p-value < 0.05

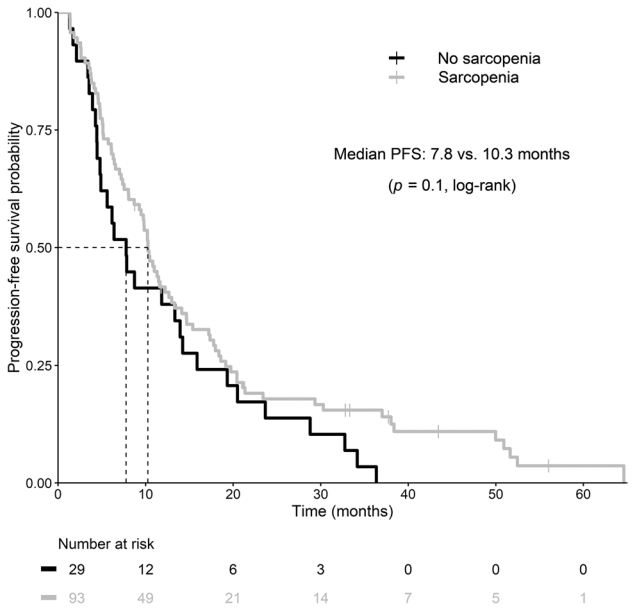

Fig. 2 Kaplan–Meier curve of PFS in patients with (gray line) and without sarcopenia (black line). The dotted line represents the median PFS (in months). PFS: progression free survival

Overall, this implies that osimertinib is a drug with a broad therapeutic range.

The absence of a positive exposure-efficacy relationship in the current dosing regimen is in line with the pharmacological characteristics found for the irreversible EGFR-TKIs. *In vitro* data showed that the turnover time for complete renewal of the EGFR protein is approximately 25 – 140 h [18]. Moreover, only low (*in vitro*) half maximal inhibitory concentrations of approximately 1.5 – 6.5 µg/L have been found for binding of osimertinib to mutated EGFR and osimertinib has a long elimination half-life of 48 h [7, 19]. All these factors taken together suggest that antitumor activity might continue even after the drug is totally cleared from the systemic circulation. Therefore, plasma concentrations would be less informative for efficacy of therapy. Moreover, if no exposure-efficacy relationship is observed in the approved dosing regimen, this might indicate that the current dose of osimertinib can be reduced. Indeed, in the phase I dose-escalation study of osimertinib and in a small retrospective study, it has been found that treatment with 40 mg QD results in a similar antitumor efficacy as for 80 mg of osimertinib [20–22].

In our study, a trend was observed where patients with low exposure to osimertinib have a higher PFS. This non-statistically significant effect between exposure and efficacy might be due to a confounding effect. It has been described that the apparent (CYP-mediated) clearance of drugs can be reduced in case of cancer-induced inflammation [23]. This inflammation may thus independently be related to both lower osimertinib clearance and a poor treatment outcome. In accordance with this, we found that patients with low exposure had more favorable prognostic markers (e.g. better WHO PS and driver mutations more sensitive to osimertinib) and a lower surrogate marker for systemic inflammation (NLR) than patients with higher osimertinib exposure.

To our knowledge, this is the first study to assess the relationship between osimertinib exposure and efficacy in a real-life cohort. Compared to the phase I/II studies of osimertinib, we included patients with a higher WHO PS, and with unstable brain metastases. We found that patients harboring primary EGFR mutations other than exon 19 del and exon 21 L858R have an increased hazard ratio for progression on osimertinib therapy. This observation is in line with study results, reporting lower antitumor activity for osimertinib (and other EGFR TKIs) in other primary EGFR mutations [24–26]. Although the observational group with other primary EGFR mutations is small (n = 10), we found a statistically significant shorter PFS, indicating that osimertinib indeed is less effective for these driver mutations.

Approximately 22.8% of patients developed a clinically relevant toxicity. Patients who experienced these toxicities were exposed to similar osimertinib plasma concentrations and a statistically significant relationship could not be distinguished. In a previous analysis, a trend was found in which higher systemic exposure to osimertinib (in terms of the area under the concentration-effect curve (AUC)) was associated with an increase in the development of rash and diarrhea (p-value not reported) [8]. Moreover, a statistically significant relationship between osimertinib exposure and QTc prolongation was found by these authors. Unfortunately, we could not confirm these results since electrocardiogram assessments were not routinely made for all patients during osimertinib therapy.

In earlier studies, it was found that sarcopenia in NSCLC patients is associated with poorer treatment outcome [10]. This effect was not found in our study, as we did not find a statistically significant effect of the presence of sarcopenia on the PFS in our study population.

Although log-linear extrapolation is an easy-to-implement method to calculate drug $C_{min,pred}$, it assumes that the measured concentrations come from blood samples

drawn after peak plasma concentrations are reached. Since the t_{max} of osimertinib is six hours, this method might underpredict the plasma $C_{min,pred}$ for samples drawn within the absorption phase of osimertinib. The use of a population pharmacokinetic model to calculate $C_{min,pred}$ (or AUC) might circumvent this limitation, although it can also introduce shrinkage towards population estimates due to the limited sampling. However, since the ratio between peak and $C_{min,pred}$ for osimertinib is reported to be only 1.6 fold [7], we assume that log-linear extrapolation is appropriate for this drug even for samples taken before the t_{max} [27]. Another limitation of this study is that a maximum of one sample per dosing interval was drawn. Therefore, the effect of other pharmacokinetic parameters, such as AUC, on efficacy and toxicity could not be investigated. Last, in this study we did not take into account the effect of the metabolite concentrations of osimertinib. AZ7550 and AZ5104 are both potent inhibitors of EGFR and their pharmacokinetic exposure could thus influence efficacy and safety outcomes [28]. Nonetheless, it has been reported that plasma levels of these drugs are less than 10% of the total drug exposure in the systemic circulation and it may be assumed that their role is limited [7].

Conclusion

This study demonstrates that osimertinib has a wide therapeutic window and that the pharmacokinetic exposure of this drug is not related to efficacy or toxicity. This study provides no rational for therapeutic drug monitoring based on plasma concentrations of osimertinib. Prospective studies should explore if lower doses of osimertinib (e.g. 40 mg QD) are sufficient to maintain efficacy.

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Data Availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest **R.J. Boosman, M. Jebbink, S.L. Groenland, B.A.M.H. van Veggel, E.F. Smit** and **A.D.R. Huitema** declare they have no conflict of interest to report.
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P. Moeskops is an employee of Quantib BV.
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