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Clinical Pharmacokinetics of Vemurafenib in BRAF-Mutated Melanoma Patients

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Keywords

vemurafenib, pharmacokinetics, therapeutic drug monitoring, routine clinical care, exposure-response, LC-MS/MS

Vemurafenib is an oral tyrosine kinase inhibitor that inhibits mutated serine/threonine protein kinase B-Raf (BRAF) and is approved as monotherapy or in combination with the MEK inhibitor cobimetinib for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.[1–3] Currently, vemurafenib is given in a fixed dose regimen of 960 mg twice daily (BID). The pharmacokinetics of vemurafenib was previously investigated in a phase 1 trial, and a mean steady-state plasma concentration of 40 ± 20 μg/mL was found.[4] Concomitant intake of food (high-fat meal) increased the C_{max} (2.5 times) and the vemurafenib plasma $AUC_{0-\infty}$ (4.7 times).[5] In addition a dose-exposure relationship has been established for vemurafenib at steady state from 240 mg BID to 960 mg BID.[6] Recent studies have shown that low vemurafenib plasma concentrations are associated with tumor progression. Funck-Brentano et al found in a study in 21 patients that the mean steady state (>14 days of treatment) plasma concentration was lower at the time of first progression (38.8 ± 19.7 μg/mL) than when the tumor was stable or in partial or complete response (56.4 ± 21.0 μg/mL).[7] In another study Kramkimel et al found that vemurafenib plasma concentrations below 40.4 μg/mL at day 15 were associated with a shorter progression-free survival (PFS).[8] The relationship between tumor progression and exposure was further established by Goldwirt et al, who found that the plasma concentrations in patients who were progressing were lower (51 ± 22 μg/mL) than those in complete or partial responders or patients with stable disease (67 ± 24 μg/mL), although this was not significant.[9] They also showed that patients with a plasma concentration >42 μg/mL had a lower risk for progressive disease than patients with a median plasma concentration below 42 μg/mL during the first year of vemurafenib treatment ($P = .005$). These results combined suggested a steady-state pharmacokinetic target of >42 μg/mL for vemurafenib.[10]

Given the strong evidence for an exposure-response relationship, therapeutic drug monitoring (TDM) might be beneficial for patients who are treated with vemurafenib. Because most data on exposure-response relationships have been obtained in clinical trials, the first step to study the potential of TDM in regular care is to evaluate the vemurafenib plasma concentrations in a cohort of patients treated with vemurafenib.

Material and Methods

Patients and Sampling

An observational study was performed in a setting at the outpatient clinic of the Antoni van Leeuwenhoek/Netherlands Cancer Institute (AvL-NKI). As part of clinical care a K_2EDTA blood sample (4 mL) was collected for pharmacokinetic monitoring from patients

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who were treated with tyrosine kinase inhibitors at each visit to the hospital, which was approved by the medical ethics committee of the AvL-NKI. All patients from whom at least 1 vemurafenib plasma concentration was available were included in this retrospective analysis.

For all patients, samples were collected approximately once a month. All plasma samples were single randomly timed samples obtained by venipuncture. The date and time of the last vemurafenib intake and the time of blood collection were recorded. Immediately after collection, whole-blood samples were centrifuged for 10 minutes at 1700*g* to isolate plasma, which was stored at nominally –20°C pending analysis.

Bioanalysis

The vemurafenib concentrations were determined using an HPLC-MS/MS method that was described previously and was validated according to the FDA and EMA guidelines for bioanalytical method validation.[11] Briefly, the sample pretreatment for plasma included liquid-liquid extraction using tert-butyl methyl ether (TBME). Vemurafenib was separated on a C18 column (Gemini C18 column, 110 Å, 50 × 2.0 mm ID, particle size 5.0 μm; Phenomenex, Torrance, California) with gradient elution and analyzed with triple quadrupole mass spectrometry (Finnigan, TSQ Quantum Ultra; Thermo Fisher Scientific, Waltham, Massachusetts). Vemurafenib proved to be stable for at least 424 days in plasma at –20°C.

Pharmacokinetics

All samples were collected after at least 15 days of vemurafenib treatment (steady state). Moreover, the elimination half-life (approximately 52 hours) of vemurafenib is very long compared to the dosing interval. Trough concentrations were estimated using the interval between the last dose intake and blood sampling and the elimination half-life.[12] This extrapolation method was used because there is currently no published population pharmacokinetic model available that would help to facilitate a Bayesian estimation approach for individual trough concentrations. In addition, the plasma concentrations were not corrected for the dosing schedule. The plasma concentrations were compared to the previously suggested target of 42.0 μg/mL.[9,10] In this study no dose adjustments were made based on plasma vemurafenib concentrations.

Patient Data Collection and Statistics

Clinical characteristics, treatment dose, and treatment duration of these patients were collected retrospectively from patient files. All calculations were performed with the R statistical software package (version 3.1.0; hppt://cran.r-project.org). A linear mixed-effects modeling was performed by a user-written PRED subroutine in NONMEM (version 7.3, ICON DevelopmentSolutions, Ellicott City, Maryland)[13] in which population mean was estimated as a fixed effect, and interpatient and intrapatient variability were estimated as random effects.

Table 1. Patient Characteristics

Number of patients	46
Number of samples	127
Samples per patient	
Number of patients (%)	
1	23 (18.1)
2	8 (6.3)
3	4 (3.1)
4	2 (1.6)
5	3 (2.4)
6	1 (0.8)
7	2 (1.6)
8	1 (0.8)
12	1 (0.8)
13	1 (0.8)
Sex	
Number of patients (%)	
Male	25 (54.3)
Female	21 (45.7)
Age (years), mean (SD)	57 (13.5)
Dosing scheme[a]	
Number of patients (%)	
960 mg BID	23 (50.0)
720 mg BID	10 (21.7)
480 mg BID	9 (19.6)
240 mg BID	1 (2.2)
720/960 mg BID[b]	2 (4.4)
240+480 mg QD[c]	1 (2.2)

[a]Patients were classified in the dosing scheme on which they were treated for the longest time period. BID, twice daily; SD, standard deviation; QD, once daily.
[b]Patients were treated with 720 mg BID or 960 mg BID, depending on toxicity.
[c]This patient was treated with 240 mg QD (morning dose) and 480 mg QD (evening dose).

Results

Patients and Samples

In total, 46 patients (25 male, 21 female) were included in this study, the patient characteristics of which are summarized in Table 1. The median age of the patients was 56 years (range 29 to 85 years). In total, 127 samples were collected with a mean of 3 samples per patient (range 1 to 13 samples).

Pharmacokinetics

The mean vemurafenib trough concentration of all collected samples was 46.2 μg/mL with a range from 8.0 μg/mL to 115.0 μg/mL and a coefficient of variation (CV) of 44.4%. In total, 60 samples (47.2%) were below the pharmacokinetic target of 42.0 μg/mL (range: 8.0 μg/mL to 41.9 μg/mL).

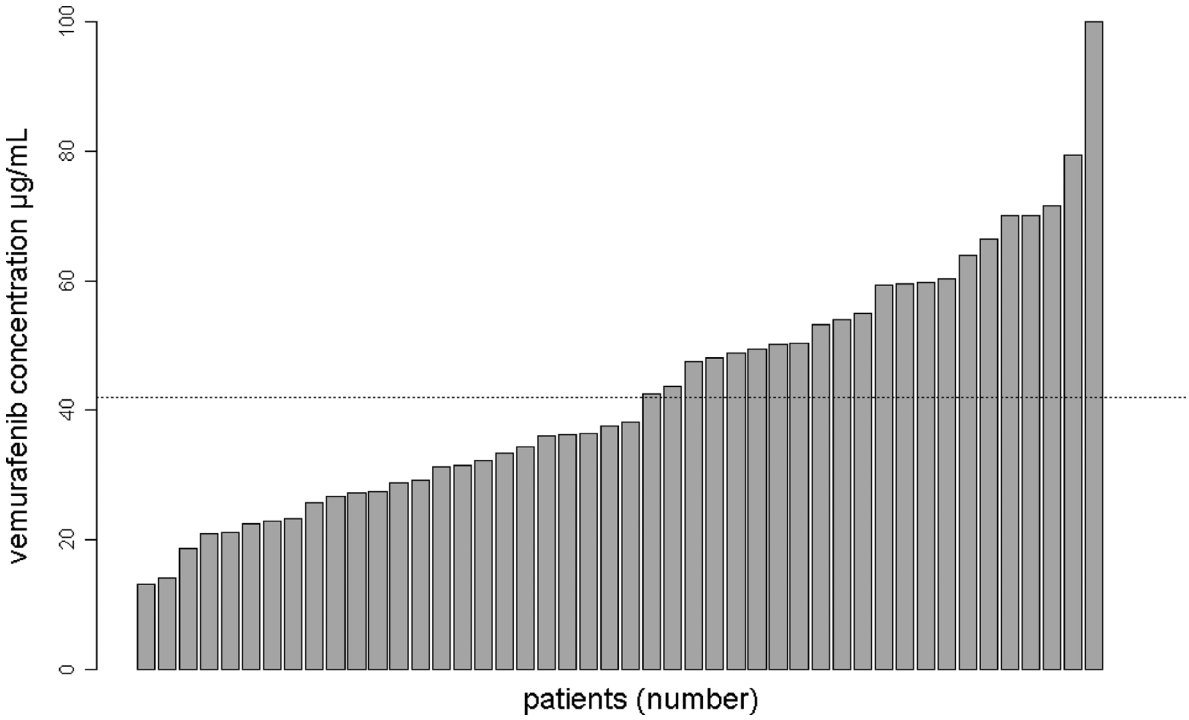

Figure 1. Distribution of the mean vemurafenib plasma concentration per patient (n = 46). The dotted line indicates the threshold of 42 μg/mL proposed by Funck-Brentano et al[7] and Goldwirt et al.[9] In total, 24 patients (52.2%) had a mean vemurafenib plasma concentration below the recommended pharmacokinetic target.

The estimated population mean was 38.9 μg/mL with an interpatient CV of 40.9% and an estimated intrapatient CV of 27.8%. The distribution of the observed mean trough concentration of each patient is shown in Figure 1. In 24 patients (52.2%) the mean observed trough concentration was below the pharmacokinetic target. Nine of these 24 patients were treated with 960 mg BID, and the other patients received dose reductions due to toxicity.

The mean treatment duration of the patients in this outpatient cohort (from the start of vemurafenib treatment to discontinuation due to disease progression or toxicity) was 11.7 months ranging from 11 days to 38 months.

Dose Adjustments

Of the 46 patients included in this study, 22 patients (48.7%) were on the recommended 960 mg BID regimen during their whole treatment (Table 1). Two patients started with 480 mg BID vemurafenib: 1 patient because of previous intolerance to dabrafenib (mean plasma concentration of 5 samples: 49.5 μg/mL) and the other patient due to renal failure, for which the patient received weekly dialysis (plasma concentration in single available sample 22.5 μg/mL). The 22 other patients (48.7%) received different dose adjustments during treatment (Table 1). In 21 patients the dose was reduced because of toxicity, which included skin toxicities (photosensitivity reaction, rash, erythema, maculopapular rash, and erythema nodosum), arthralgia, increased liver enzymes, uveitis, headache, neutropenia, and fatigue. Two patients received a dose increase from 960 mg BID to 1200 mg BID when disease progression was established. These dose increases did not result in higher vemurafenib plasma concentrations (from 36.7 μg/mL to 37.9 μg/mL and from 79.4 μg/mL to 39.4 μg/mL). For 3 additional patients plasma samples were collected before and after dose reductions. These dose reductions did not result in proportional lower exposures (720 mg BID to 480 mg BID resulted in an increase from 44.4 μg/mL to 64.4 μg/mL; 960 mg BID to 480 mg BID resulted in a decrease from 61.3 μg/mL to 54.9 μg/mL; 960 mg BID to 720 mg BID resulted in a decrease from 115.0 to 83.8 μg/mL).

Discussion and Conclusions

In this study we investigated the vemurafenib plasma concentrations of an outpatient melanoma patient population. The previously established target concentration of 42.0 μg/mL was compared to the plasma concentrations in this population.[9,10] More than half of the patients were underexposed to vemurafenib with an increased risk for treatment failure. TDM in combination with dose individualization might be a valuable tool to optimize vemurafenib treatment. However because

of the observed toxicity, a dose increase to optimize treatment is possible in only a limited number of patients, and the administration of doses higher than 960 mg BID should first be further explored in a clinical trial. If the administration of doses higher than 960 mg BID would lead to higher plasma concentrations, this could be potentially beneficial to 9 of the 24 patients who were underexposed.

This is the first study in which vemurafenib plasma concentrations from patient care were reported. We found a high fraction of patients potentially undertreated. Furthermore, a high number of patients (51.3%) received a dose reduction in our cohort compared to other studies. In the BRIM-3 study, 38% of the patients received a dose reduction.[1] Kramkimel et al reported that 27% of the patients received a dose reduction, and 12% of the patients stopped treatment due to toxicities,[8] and Funck-Brentano et al reported that 44% of the patients received a dose reduction.[7] The toxicities leading to dose reductions were similar to the toxicities observed in previous studies. In this study dose adjustments did not result in dose-proportional changes in vemurafenib exposure, which is not in line with the previously established dose-exposure relationship for vemurafenib at steady state from 240 mg BID to 960 mg BID.[6] Higher doses were, however, not investigated. Because a dose-exposure relationship is an important prerequisite for TDM, this should be further explored in a study investigating dose adjustments in patients with low ($<42.0\ \mu$g/mL) plasma concentrations.

The interpatient (CV 40.9%) and intrapatient (CV 27.8%) variability found in this study were comparable to previously reported data.[7,8] Several parameters may account for this large interpatient variability. The intake of vemurafenib on an empty stomach may reduce the exposure to vemurafenib significantly compared to intake after a meal.[5] This possibility was, however, not monitored in this study.

This study shows that more than half of the melanoma patients treated with vemurafenib are potentially underexposed. The potential of dose individualization in combination with TDM for treatment optimization should first be further explored before this protocol can be implemented in clinical practice.

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