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ORIGINAL ARTICLE

Therapeutic drug monitoring of small molecule kinase inhibitors in oncology in a real-world cohort study: does age matter?

Correspondence Marie-Rose B.S. Crombag, PharmD, Department of Pharmacy & Pharmacology, Netherlands Cancer Institute and MC Slotervaart, Louwesweg 6, 1006 BK Amsterdam, The Netherlands. Tel.: +31 20 512 7924; Fax: +31 20 512 4753; E-mail: m.crombag@nki.nl

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Marie-Rose B.S. Crombag[1,2], Jacobine G.C. van Doremalen[1,3], Julie M. Janssen[1,2], Hilde Rosing[1], Jan H.M. Schellens[2,3,4], Jos H. Beijnen[1,2,3], Neeltje Steeghs[2,4] and Alwin D.R. Huitema[1,2,5]

[1]Department of Pharmacy & Pharmacology, Netherlands Cancer Institute and MC Slotervaart, Amsterdam, The Netherlands, [2]Division of Pharmacology, Netherlands Cancer Institute, Amsterdam, The Netherlands, [3]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht, The Netherlands, [4]Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands, and [5]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

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AIM

Pharmacokinetics of small molecule kinase inhibitors (KIs) used in cancer treatment may alter with increasing age, but results are conflicting. This study aims to compare exposure to KIs between older and younger patients (≥70 and <70 years) in clinical practice.

METHODS

KI plasma concentrations of routinely treated patients were measured using validated assays. Calculated trough concentrations were compared in both age groups. For KIs with a clinically meaningful target concentration (erlotinib, imatinib, pazopanib, sunitinib and vemurafenib), influence of older age on target attainment was assessed.

RESULTS

We analysed 616 samples from 454 patients (median age: 61; range 20–93 years), treated with dabrafenib (n = 105), erlotinib (n = 49), imatinib (n = 165), pazopanib (n = 63), sunitinib (n = 87), trametinib (n = 95) and vemurafenib (n = 52). Older age did not significantly influence exposure to erlotinib, imatinib, pazopanib, sunitinib, trametinib and vemurafenib. Elderly patients had significantly higher dabrafenib trough concentrations than younger patients (P = 0.02; 62 ng ml^{-1} (coefficient of variation [CV] 41%), *vs.* 53 ng ml^{-1} (CV 46%), respectively). For KIs with a predefined target concentration, 68% of older and 61% of younger patients reached target.

CONCLUSIONS

In this real-world study, exposure to most included KIs was comparable in older and younger patients, except for dabrafenib, which showed higher exposure in older patients. In the absence of an absolute target for this KI, clinical relevance remains unclear. For all other included KIs, our data suggest no clinically relevant influence of older age on KI exposure.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Adequate systemic exposure is a prerequisite for the treatment efficacy and safety of KIs.
- Exposure to KIs may differ between older and younger patients due to progressive reduction in organ functions and co-morbidities.

WHAT THIS STUDY ADDS

- Exposure to most included KIs was comparable in older and younger patients, except for dabrafenib, which showed higher exposure in older patients.
- In the absence of an absolute target for this KI, clinical relevance remains unclear.
- For all other included KIs, our data suggest no clinically relevant influence of older age on KI exposure.

Introduction

Elderly are increasingly frequently diagnosed and treated for cancer [1]. Treatment-related toxicity is a major concern in older patients receiving classical cytotoxic agents [2]. There was hope that the introduction of new targeted therapies, such as small molecule kinase inhibitors (KIs), might favour the elderly patient population, as less off-target toxicity was expected due to the relatively high target specificity of these agents.

Adequate systemic exposure is a prerequisite for the treatment efficacy and safety of these oral agents. However, inter-individual variability in pharmacokinetics of KIs is extensive, thus complicating dose–response assessments [3, 4]. This variability may, in part, be ascribed to patient characteristics, such as vital organ functions, drug and food interactions, pharmacogenetic heterogeneity between patients and treatment adherence. Therefore, therapeutic drug monitoring (TDM) may be a valuable tool to reach target concentrations in order to optimize treatment outcomes in the heterogeneous group of patients treated with KIs.

For multiple KIs, a minimal plasma concentration threshold has been established, above which improved efficacy was observed. Target trough concentrations were advocated for sunitinib, imatinib, pazopanib, vemurafenib, crizotinib, erlotinib and gefitinib, and were often determined after market approval [3–5]. Thus far, no target concentrations are available for other KIs, warranting further studies to evaluate exposure efficacy and tolerability of these agents [3, 4, 6, 7].

In older patients, multiple physiological parameters are altered, which may substantially influence absorption, distribution, metabolism and excretion of KIs. Other factors may also contribute to the complexity of treatment, including co-morbidities, polypharmacy and performance status [8].

As clinical trial results cannot plainly be extrapolated from younger to older patients, the European Union, Japan and the United States have implemented regulatory guidance mandating sufficient inclusion of geriatric patients in clinical study programmes [9]. As a result, several clinical trials and subsequent analyses by the regulatory agencies have evaluated the influence of older age on pharmacokinetics-pharmacodynamics (PK-PD) of KIs. These analyses showed no clinically relevant age-related differences in the PK of multiple KIs as, for example, is the case for trametinib [7, 10]. However, both the FDA and EMA emphasized that insufficient information is available for many KIs, e.g. including dabrafenib, pazopanib, trametinib and vemurafenib, to properly assess potential differences between the elderly and their younger peers [11–13].

Results of these clinical trials were disputed by a recent real-world cohort study of patients with non-small-cell lung cancer (NSCLC) treated with gefitinib or afatinib [14], showing improved effectiveness in elderly patients. The authors hypothesized that this difference may be driven by increased plasma concentrations in elderly patients, due to the increased use of co-medication. However, this study lacked PK data to support their claim. Conflicting results were also reported on the influence of older age on the PK of erlotinib [15, 16].

Due to various conflicting study results and a paucity of real-world data, i.e. data collected under real-world practice circumstances, the influence of older age on PK of KIs in clinical practice remains undetermined. Therefore, this study was designed to (1) evaluate any PK differences between elderly and younger patients (≥70 years *vs.* <70 years old) treated with a KI, (2) compare target attainment, if applicable, per KI between these age groups, and (3) evaluate factors that may influence the impact of age on KI exposure in our study population.

Methods

Patients

All patients receiving a KI at the Netherlands Cancer Institute (NKI, Amsterdam, The Netherlands) between April 2011 and April 2017 were eligible for inclusion in this study, if at least one KI blood sample was available. These blood samples were collected as part of clinical practice for TDM purposes from all patients treated with a KI at the NKI. Blood withdrawals were single randomly timed samples collected in conformance with standardized procedures using a venipuncture. To preclude bias of dose adjustments based on reported TDM concentrations, we included only the first measured plasma concentration during steady-state of each drug per patient. The use of multiple different KIs concomitantly or sequentially by one patient was permitted. Patient characteristics, KI dosing and dose reduction motives, treatment indication, laboratory values at the time of blood withdrawal for TDM, and interacting medication were collected from the patients' electronic records. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula [17]. A patient's age was calculated as the age at the time of blood sampling.

In this study a cut-off of 70 years was used, resulting in two age groups, namely elderly patients defined as those being 70 years or older, and younger patients defined as those under the age of 70. A minimum of 10 patients per age group for each KI was set for inclusion of the KI in the final analysis. As part of routine care, for all patients a full medication reconciliation was performed at each moment of medication dispensing. All potentially relevant drug–drug interactions were evaluated according to the guidelines of the Royal Dutch Pharmacists Association [18]. In the case of relevant drug–drug interactions, the hospital pharmacist and prescribing physician were responsible for taking appropriate action. Conduct of this study was approved by the Medical Research Ethics Committee of the Netherlands Cancer Institute, Amsterdam, The Netherlands.

Bioanalysis

Analyses of KIs and their relevant metabolites (for sunitinib) in plasma were performed using previously validated high-performance liquid chromatography coupled with triple quadrupole mass spectrometry (HPLC-MS/MS) detection methods [19, 20].

Trough concentration estimation

Trough levels were calculated using the algorithm reported by Wang *et al*. [21], taking into account the time after the last dosing event, time of sampling and the mean elimination half-life. In this study, this algorithm was used for erlotinib, imatinib, pazopanib, sunitinib, trametinib and vemurafenib, because linear elimination was reported for these KIs in the dose ranges included in this cohort study [7, 11, 22–26]. The time of the last dosing event and time of withdrawal had to be documented in order to calculate the time after dose (TAD). If the calculated TAD was greater than the time taken to reach the maximal plasma concentration (T_{max}) and before the scheduled next dosing event (with a half-hour deviation range), thus sampled during the drug's elimination phase, the trough concentration was estimated per KI. If sampling occurred before T_{max}, the sample was excluded from the final analysis. Calculations for once and twice daily dosing regimens were as follows:

$$C_{trough} = C_{measured} * 0.5^{\left(\frac{\tau - TAD}{t^{1/2}}\right)}$$

where the calculated trough concentration (C_{trough}), and the measured plasma concentration ($C_{measured}$) are expressed as concentrations in ng ml^{-1}. The time of dosing interval (τ) and TAD are in hours, with TAD defined as the time in hours between the last dosing event and blood withdrawal. T_{max} and elimination half-life ($t_{1/2}$) are the values reported per KI by the regulatory authorities, as depicted in Table 1. For sunitinib the calculated trough concentration comprised the sum of the calculated C_{trough} of sunitinib and its metabolite N-desethyl-sunitinib.

Because inducible clearance after multiple dosing of dabrafenib was observed, the trough concentration of dabrafenib was estimated using a previously published two-compartment model including initial clearance and inducible clearance [27]. From this model Bayesian estimates for the trough concentration were generated.

Statistical analysis

Descriptive statistics were used to depict patient characteristics, time after the last dose event, and laboratory values at the time of blood withdrawal for TDM. The Wilcoxon rank-sum test was used to evaluate the influence of older age (≥70 *vs*. <70 years) on trough concentrations and administered dose of each included KI. If applicable, target attainment between patients ≥70 years and those aged <70 years was assessed using Fisher's exact test. We assessed the influence of the covariates gender and tumour type on KI exposure, except for dabrafenib because significant covariates were

Table 1

Drug information per included KI

KI	Indication[a]	Standard reported dose[b]	Predefined target trough concentration (ng ml^{-1})	T_{max} (h)	Elimination half-life (h)
Dabrafenib	Melanoma	150 mg BID	NA	2	8 [6]
Erlotinib	NSCLC	150 mg QD	>500 [3]	4	36 [22]
Imatinib	GIST	400 mg QD	>1100 [3]	2.5	18 [23]
Pazopanib	RCC Sarcoma	800 mg QD	>20.5[c] [3]	4	31 [13]
Sunitinib + N-desethyl-sunitinib[d]	RCC GIST	50 mg QDC, 37.5 mg QDS	>50 [3], >37.5–50 [3]	6	50/80[e] [28]
Trametinib	Melanoma	2 mg QD	NA	1.5	127 [7]
Vemurafenib	Melanoma	960 mg BID	>42[c] [4]	4	52 [29]

BID, twice daily; GIST, gastrointestinal stromal tumor; NA, not applicable; QD, once daily; QDC, once daily continuously; QDS, once daily with a stopping period; RCC, renal cell carcinoma; T_{max}, time taken to reach the maximal plasma concentration

[a]Including indications that were present in the cohort

[b]Most frequently reported dose in the cohort

[c]Target trough concentration depicted as × 10^3 ng ml^{-1}, i.e. in μg ml^{-1}

[d]Trough concentrations are combined trough concentrations of sunitinib and N-desethyl-sunitinib

[e]Approximate elimination half-life of sunitinib is 50 h and of N-desethyl-sunitinib is 80 h

already included in the model used to calculate trough concentrations. Additionally, the impact of age on KI exposure was evaluated as a continuous variable using regression analyses. A *P*-value of <0.05 was considered statistically significant.

Results

In total, blood samples from 715 patients receiving KI treatment between April 2011 and April 2017 were evaluable. The KIs afatinib, axitinib, crizotinib, gefitinib, lapatinib, osimertinib and regorafenib were excluded from our database because the minimal number of 10 patients per age group was not reached. Our final cohort contained 616 first blood samples from 454 patients (use of different KIs concomitantly or sequentially was permitted). Included KIs were dabrafenib (n = 105), erlotinib (n = 49), imatinib (n = 165), pazopanib (n = 63), sunitinib (n = 87), trametinib (n = 95) and vemurafenib (n = 52), of which 16%, 39%, 28%, 19%, 25%, 14% and 19%, respectively were ≥70 years old. An overview of all included KIs, indications as reported in this cohort, most frequently reported dose in the cohort, and if applicable, proposed target concentration, is given in Table 1.

The median age of patients included in the final analysis was 61 years (range 20–93 years), and 46% of patients were female. Twenty-three percent of the total cohort consisted of patients aged 70 years or older, per drug varying from 14 to 39%. Gender, the timing of blood withdrawal after KI administration (i.e. time after dose [TAD]) and hepatic laboratory values were comparable between both age groups. Older patients had significantly lower serum albumin and eGFR values (P = 0.004 and P < 0.001, respectively) than their younger counterparts, as shown in Table 2.

For erlotinib, imatinib, pazopanib, sunitinib, trametinib and vemurafenib, comparable trough concentrations were determined between older and younger patients, as shown in Figure 1 and Table 3. For sunitinib, no difference in exposure was observed in the total group. Similarly, no difference was observed when stratified for indication (mRCC or GIST). Trough plasma concentrations of dabrafenib were significantly higher in older patients than in their younger peers (P = 0.02), as shown in Figure 1 and Table 3. The median trough concentration of dabrafenib was 62 ng ml^{-1} in the elderly group (IQR 54–87 ng ml^{-1}, CV 41%), and 53 ng ml^{-1} in their younger peers (IQR 46–66 ng ml^{-1}, CV 46%), as shown in Table 3.

The proportion of patients reaching their predefined efficacy target was comparable between both age groups, with 68% of elderly patients and 61% of younger patients reaching the target (P = 0.17), as shown in Table 4. Although no clinically relevant target concentration has been established for dabrafenib, a pooled population PK analysis of four clinical trials reported a typical pre-dose concentration of 46.6 ng ml^{-1} [27]. This plasma concentration was reached by 94% of older patients and 74% of younger patients, not reaching significance (P = 0.11). Likewise, for trametinib, no established target concentration was available, although a Phase II trial reported longer progression-free survival in patients with a target concentration above 10.6 ng ml^{-1} [10]. This proposed target was reached by 77% of older patients and 48% of younger patients, not reaching statistical significance (P = 0.07).

Most frequently prescribed doses in the cohort reflect the registered doses by regulatory agencies [6, 7, 23, 28, 29], as shown in Table 1. Prescribed doses of most KIs were comparable between both age groups, except for pazopanib and sunitinib, of which the elderly patients received significantly lower doses. For pazopanib, a quarter of all patients received a dose lower than 800 mg once daily, with older patients receiving a median dose of 600 mg compared to 800 mg in younger patients (P < 0.001). Patients' electronic records revealed that pazopanib dose reductions were mainly due to fatigue, gastrointestinal adverse events and hypertension. For sunitinib, 16% of all patients received a dose lower than the standard reported doses. In the total sunitinib group, older patients received a median dose of 37.5 mg sunitinib compared to a median dose of 50 mg sunitinib in younger patients (P = 0.003). This difference was driven only by patients with renal cell carcinoma,

Table 2

Patients' characteristics

Parameter	≥ 70 years	< 70 years	*P*-value
Total number of patients	454		
***n* (%)**	106 (23)	348 (77)	
Age (years), median [range]	74 [70–93]	57 [20–69]	
Female, *n* (%)	50 (47)	159 (46)	0.82
Total number of samples	616		
Time after dose (h)[a], median [IQR]	11 [5–20]	12 [5–19]	0.79
Organ functions at TDM sampling			
ALT (U l^{-1}), median [IQR]	23 [18–33]	23 [17–36]	
<ULN (%)	87	83	0.36
≥ULN (%)	13	17	
Total bilirubin (μmol l^{-1}), median [IQR]	6 [4–9]	5 [3–7]	
<ULN (%)	92	95	0.32
≥ULN (%)	8	5	
eGFR (ml min^{-1} 1.73 m^{-2}), median [IQR]	66 [48–81]	79 [65–91]	
>ULN (%)	55	82	<0.001*
≤ULN (%)	45	18	
Albumin (10^{9} l^{-1}), median [IQR]	40 [37–44]	43 [40–45]	
≥ULN (%)	87	96	0.004*
<ULN (%)	13	4	

ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate, calculated using the Modification of Diet in Renal Disease (MDRD) formula; IQR, interquartile range 25–75%; ULN, upper limit of normal

*P-value reached significance

[a]With the T_{max} as the minimal time after dose per KI

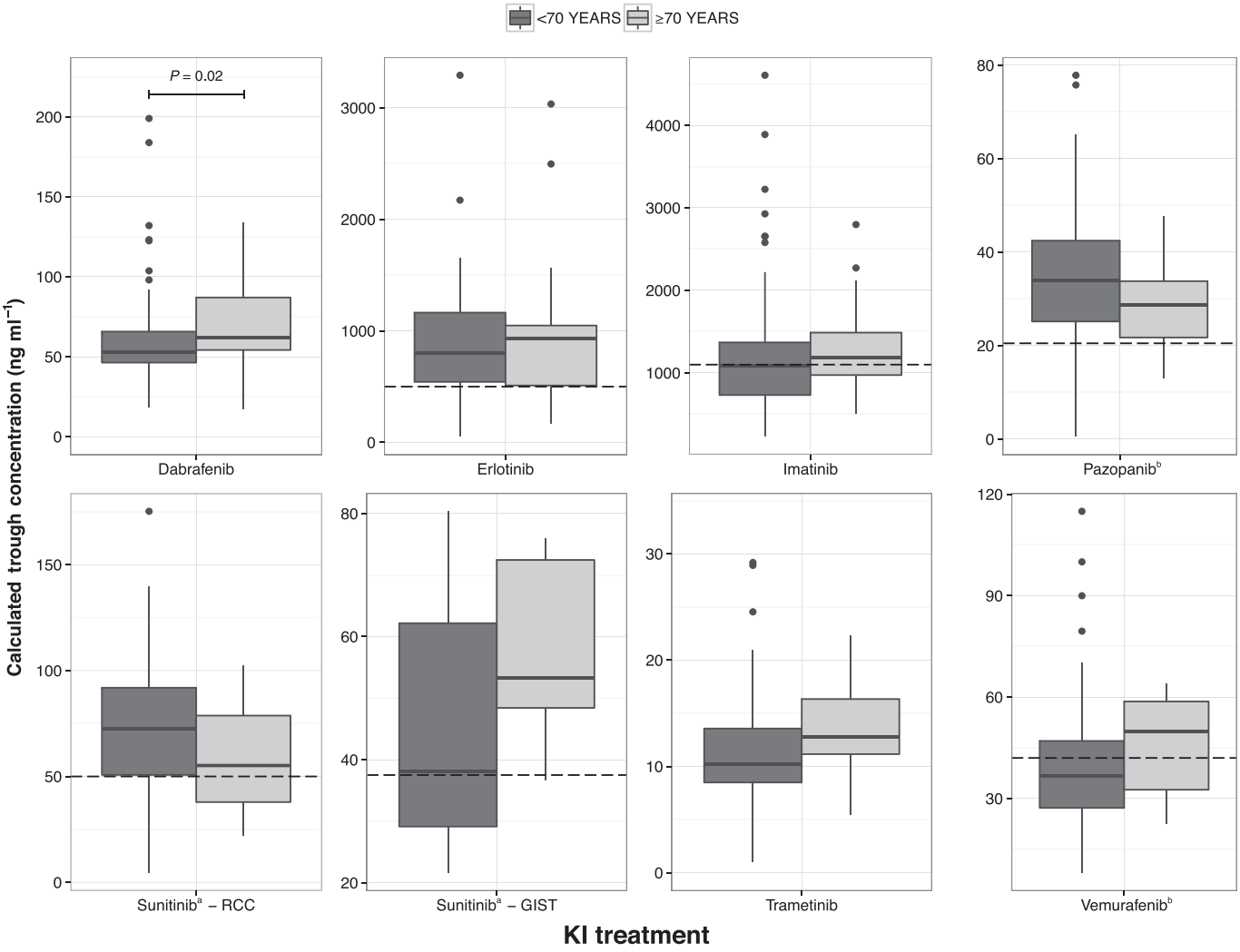

Figure 1

Box-plots of KI trough concentrations per age group, with the dashed lines representing the target concentration, if applicable. [a]Combined trough concentrations of sunitinib and N-desethyl-sunitinib. [b]Target trough concentration depicted as $\times 10^3$ ng ml^{-1}, i.e. in μg ml^{-1}

who all received sunitinib with a stopping period per treatment cycle. All GIST patients received sunitinib in a continuous schedule, with a median dose of 37.5 mg in both age groups ($P = 0.77$). Evaluation of patients' electronic records revealed that sunitinib dose reductions were caused by toxicity, mainly including fatigue, hand-foot syndrome, gastrointestinal and haematological adverse events.

Exploratory univariate regression analyses showed that neither gender, nor tumour type significantly influenced KI exposure. Additionally, age treated as a continuous variable did not influence exposure to any included KI in regression analyses, as shown in Figure 2.

Discussion

In this real-world cohort, older age had no significant influence on KI trough concentrations, except for dabrafenib, in which higher exposure in elderly patients was observed. In the absence of an absolute target for this KI, clinical relevance of this finding remains unclear. For all KIs with a predefined target concentration, the frequency of target attainment was similar between both age groups. The administered dose of most KIs was not age-dependent. For pazopanib and sunitinib, a significantly lower dose was prescribed to older patients than to their younger peers. These lower doses resulted in a non-significantly lower percentage of older patients reaching the predefined target concentration for these two KIs.

Approximately one-third of our total patient cohort did not reach the proposed target concentration of their administered KI. This warrants routine use of TDM and subsequent dose individualization in these patients using KIs in clinical practice, in order to realize optimal KI treatment outcomes in a timely manner [3, 4, 30, 31]. Hence, randomly timed blood samples are withdrawn from all patients treated with a KI at the NKI as part of clinical practice. To evaluate all

Table 3

Trough concentrations per KI compared between older and younger patients

KI	Patient inclusion (*n*, (%))		Median trough concentration (ng ml^{-1}, [IQR])		
	≥70 years	<70 years	≥70 years	<70 years	*P*-value
Dabrafenib	17 (16)	88 (84)	62 [54–87]	53 [46–66]	0.02*
Erlotinib	19 (39)	30 (61)	935 [510–1048]	802 [543–1164]	0.59
Imatinib	47 (28)	118 (72)	1183 [973–1488]	1082 [731–1369]	0.06
Pazopanib	12 (19)	51 (81)	29 [22–34][b]	34 [25–42][b]	0.26
Sunitinib + N-desethyl-sunitinib[a]	22 (25)	65 (75)	54 [38–75]	63 [43–88]	0.26
Trametinib	13 (14)	82 (86)	13 [11–16]	10 [8–14]	0.08
Vemurafenib	10 (19)	42 (81)	50 [33–59][b]	37 [27–47][b]	0.21

IQR, interquartile range 25–75%
[a]Combined trough concentrations of sunitinib and N-desethyl-sunitinib
[b]Median trough concentration depicted as ×10^3 ng ml^{-1}, i.e. in μg ml^{-1}
**P*-value reached significance

available real-world data, trough concentrations of these KIs were calculated using the aforementioned algorithm [21]. This algorithm presumes a general exponential decline in plasma concentration based on an established elimination half-life. Because linear elimination was reported for all KIs, except for dabrafenib, in the included dose ranges, use of this algorithm appeared feasible [7, 11, 22–26]. This method was also used to determine the exposure–survival relationship of pazopanib and is implemented for TDM purposes at the NKI [32]. For dabrafenib, inducible clearance after multiple dosing was reported [6]. Therefore, the trough concentration of dabrafenib was calculated using a previously published two-compartment model including both initial clearance as well as inducible clearance [27].

Table 4

Target attainment in older and younger patients treated with KIs with a predefined target

KI	Target attainment (%)		*P*-value
	≥70 years	<70 years	
Erlotinib	79	77	1
Imatinib	64	49	0.12
Pazopanib	83	86	1
Sunitinib + N-desethyl-sunitinib (total)	59	69	0.44
RCC	53	76	
GIST	80	50	
Vemurafenib	70	38	0.09
TOTAL	68	61	0.17

With all target attainment percentages representing the percentage of patients per age group that reached the predefined clinically meaningful target concentration

For gefitinib and afatinib, insufficient data were available to counter or support the hypothesis of Rossi *et al*. that higher exposure is the basis for their observed improvement in efficacy in older lung cancer patients treated with these KIs [14]. However, comparable exposure to most included KIs in this real-world study regardless of age are in line with the majority of previous clinical trials and observational studies, showing no clinically relevant impact of older age on KI exposure [15, 16, 33–36]. Elderly patients may be more prone to treatment-related adverse events, which may be due to higher exposure or a greater treatment sensitivity. Overall, no major age-related differences in the safety profiles of included KIs were reported by the regulatory agencies [11–13, 23, 28, 37, 38]. For dabrafenib, however, more older patients had adverse events that led to dose reduction and interruption compared to their younger peers [37]. But regulatory agencies also stressed that an insufficient number of older patients was included in most clinical trials to draw firm conclusions [11–13, 38].

For dabrafenib, a pooled population PK analysis showed that age had no significant influence on PK [27]. However, we determined a significantly higher dabrafenib exposure in the older patient group. The relatively high dispersion of the dabrafenib plasma concentrations in our cohort is in line with findings from previous trials, in which interindividual variability ranged from 53% to 160% [6, 27]. This variability remains largely unexplained in population PK analyses taking multiple intrinsic and extrinsic factors into account [6, 27], but may be partly ascribed to a high variability in absorption. In the absence of a target concentration for dabrafenib, clinical relevance of higher exposure in older patients remains unclear. A pooled population PK analysis reported a typical steady-state dabrafenib trough concentration of 46.6 ng ml^{-1} [27], which was reached by a comparable proportion of older and younger patients treated with dabrafenib in this study. For trametinib, there is also no established target concentration available, although a Phase II trial reported higher efficacy in patients above a target concentration of 10.6 ng ml^{-1} [10]. This

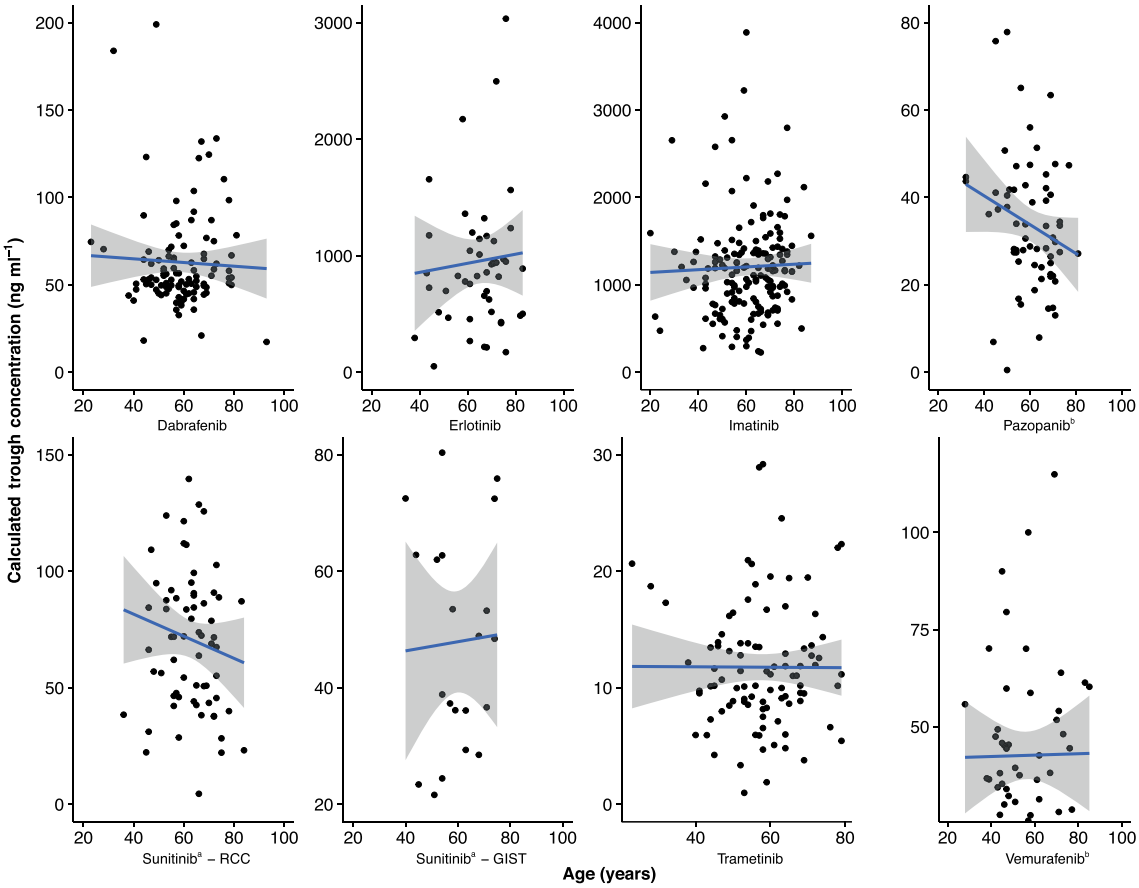

Figure 2

KI trough target concentrations *vs*. age as a continuous variable, with dots representing calculated KI trough concentration per patient, and the line fitted using a linear model. [a]Combined trough concentrations of sunitinib and N-desethyl-sunitinib. [b]Target trough concentration depicted as $\times 10^3$ ng ml^{-1}, i.e. in μg ml^{-1}

target was reached by a comparable proportion of older and younger patients using trametinib.

Exploratory covariate evaluation revealed that neither gender nor tumour type significantly affected exposure to any included KI. Due to its retrospective design, data on performance status, and co-morbidities could not be fully extracted from the patients' medical records. This is a limitation of the current study. However, no association has been determined between performance status and anticancer treatment toxicity in older patients [39]. Furthermore, per protocol, for all patients, full standardized medication reconciliation and subsequent check on potential interacting medication was performed. Therefore, the probability that any differences in age were caused or masked by differences in interacting medication in elderly patients is considered extremely small. It should be kept in mind, however, that the clinical relevance of multiple interacting medications on KI exposure remains uncertain and adequate evaluation of its impact on KI exposure in a retrospective setting is challenging. Although overlapping, older patients had significantly lower serum albumin and eGFR values. All KIs appear to be highly protein bound, but clinical relevance of lower serum albumin on KI exposure has not been fully established. Exposure to imatinib was reported to increase with diminished renal function [23], but despite lower eGFR values in older patients, imatinib exposure was not age-related.

In this study we used a cut-off of 70 years for the elderly group. This threshold value of 70 years is commonly used to evaluate the impact of age on anti-cancer treatment, as, for example, is the case for erlotinib [40], because at this age occurrence of diminished organ functions and co-morbidities tends to rise. Additionally, age was also evaluated as a continuous variable in exploratory covariate analysis. Age handled as a continuous variable did not significantly influence exposure to any included KI.

Conclusion

In this real-world study, no impact of older age on the exposure of most included KIs was observed, except for dabrafenib, for which higher exposure in older patients was observed. In the absence of an absolute target concentration for this KI, clinical relevance of this finding remains unclear. For all other included KIs, our data suggest no clinically relevant influence of older age on KI exposure.

Competing Interests

There are no competing interests to declare.

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