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ORIGINAL RESEARCH ARTICLE

Individualized Dosing Patterns in the Treatment of Older Patients with Gastrointestinal Stromal Tumors: Results of a Registry-Based Observational National Cohort Study Including 871 Patients

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Abstract

Background While the effectiveness of tyrosine kinase inhibitors (TKIs) seems similar in older patients with gastrointestinal stromal tumors (GIST) compared with younger patients, toxicities in older patients treated with TKIs more often lead to discontinuation of treatment.

Objective To better understand the age-related pharmacology and pharmacodynamic differences in patients with GIST treated with TKIs, the primary aim of this study was to evaluate TKI dosing patterns in older patients with GIST, while the secondary aims were to evaluate differences in imatinib trough plasma concentrations between age groups and to compare the overall survival (OS) in patients with and without dose reductions in all treatment lines in a palliative setting.

Methods Patients (18 years of age or older) with histologically proven GIST diagnosed between January 2009 and June 2021 and treated with one or more lines of TKIs were selected from the Dutch GIST Registry (DGR) database. Age groups were divided into younger patients (age <70 years) and older patients (age ≥70 years). All imatinib trough plasma concentrations of blood withdrawals taken from initiation of imatinib until a maximum of 1 year of treatment with imatinib were collected. Reasons for first adjustment of treatment were classified as adverse event, dose modification, progressive disease and other reasons. The next treatment steps after first adjustment of treatment were defined as dose escalation, dose reduction, dose interruption, or end of treatment. The association of dose reduction and OS was analyzed using the landmark approach.

Results Overall, 871 patients were included in this study, including 577 younger patients and 294 older patients. Older patients more often had an adverse event as the reason for first adjustment of treatment with both imatinib (45.6%; $p < 0.001$) and sunitinib (58.6%; $p = 0.224$) compared with younger patients (19.5% and 42.7%, respectively). Adjustment of imatinib and sunitinib after starting on a standard dose because of an adverse event most often resulted in dose reduction in both age groups. Median trough plasma concentrations of all samples taken within the first year after initiation of imatinib were higher in older patients (1228 ng/mL, interquartile range [IQR] 959–1687) compared with younger patients (1035 ng/mL [IQR 773–1377]; $p < 0.001$). No significant differences were seen between OS in patients with or without dose reduction in all treatment lines (imatinib: $p = 0.270$; sunitinib: $p = 0.547$; and regorafenib: $p = 0.784$).

Conclusion Older patients showed higher imatinib trough plasma concentrations compared with younger patients and also had earlier and more often adverse events as the reason for first adjustment of treatment with imatinib followed by dose reduction. However, in a landmark analysis, patients with imatinib dose reductions had no poorer outcomes compared with patients not requiring a dose reduction.

1 Introduction

Since activating receptor tyrosine kinase (KIT) mutations were first identified in gastrointestinal stromal tumors (GIST), the journey of therapeutic KIT targeting started [1]. The proto-oncogene c-KIT encodes a receptor tyrosine kinase protein. In GIST, a gain-of-function mutation leads to continuous activation of c-KIT, inducing abnormal cell growth. Tyrosine kinase inhibitors (TKIs) inhibit the activity of c-KIT by preventing the signaling that is needed for phosphorylation and activation of c-KIT by blocking the ATP-binding pocket [2].

Extended author information available on the last page of the article

Key Points

Older patients with gastrointestinal stromal tumors (GIST) had earlier and more often adverse events as the reason for first adjustment of treatment with imatinib followed by dose reduction compared with younger patients.

Older patients with GIST had higher imatinib trough plasma concentrations compared with younger patients.

Overall survival in patients with GIST with or without dose reduction did not differ significantly.

Over the last two decades, TKIs such as imatinib, sunitinib, and regorafenib have been implemented in the treatment of patients with GIST [3–5]. Median overall survival (OS) increased over several years. The median progression-free survival of patients treated with imatinib, sunitinib and regorafenib is 2 years, 8.3 months and 4.8 months, respectively [6–9]; however, a large proportion of patients treated with TKIs suffer from adverse events such as fatigue, nausea, diarrhea, (periorbital) edema and hand-foot syndrome, affecting their quality of life [10–15]. In clinical practice, adverse effects of TKIs are common reasons for discontinuation of treatment, dose reductions or even switching to subsequent treatment lines. Long-term treatment with imatinib in a continuous dosage showed decreasing trough plasma levels combined with less adverse events over time. On the other hand, lower trough plasma levels of imatinib are related to worse outcomes such as disease progression [16]. Therefore, to better understand the exposure-response and exposure-toxicity relationship of treatment with TKIs in patients with GIST and to improve personalized medicine, therapeutic drug monitoring (TDM) was implemented in the Dutch GIST standard-of-care guidelines as a tool to optimize TKI dosing [17].

The median age of patients with newly diagnosed GIST varies from 60 to 70 years [18]. Particularly in older patients, the safety and tolerability of treatment with TKIs remains poorly understood. Multimorbidity and polypharmacy are important risk factors for adverse drug reactions; however, in current research, important factors such as frailty have not been taken into account. While the effectiveness of TKIs seems similar in older patients with GIST compared with younger patients, toxicities in older patients more often lead to treatment discontinuation [19, 20]. As quality of life is often prioritized above quantity of life in older patients, optimization of treatment with TKIs is an important goal in this subgroup [21].

Therefore, to better understand the age-related pharmacology and pharmacodynamic differences in patients with GIST treated with TKIs, the primary aim of this study was to evaluate TKI dosing patterns in older patients with GIST, while the secondary aims were to evaluate differences in trough plasma concentrations of imatinib between age groups and to compare OS in patients with and without dose reductions in all treatment lines in a palliative setting.

2 Methods

The Dutch GIST Registry (DGR) includes all adult patients with GIST treated in one of the collaborating Dutch GIST centers (UMC Groningen, LUMC Leiden, Erasmus MC Rotterdam, RadboudUMC Nijmegen and the Netherlands Cancer Institute, Amsterdam) since January 2009. This study was approved by the local review boards of centers participating in the DGR.

2.1 Study Population

Patients (18 years of age or older) with histologically proven GIST and treated with one or more lines of TKIs were retrospectively selected from the DGR database. All patients diagnosed between January 2009 and June 2021 were included. Patients who were not treated with one or more selected TKIs (imatinib, sunitinib or regorafenib) as well as patients who were lost to follow-up (FU) were excluded.

2.2 Variables

Baseline characteristics (i.e., sex, age, location of primary tumor, primary tumor size and 'presentation at registry'), molecular pathology reports (including mutation status), and treatment and outcome measures were collected from the DGR database. 'Presentation at registry' was considered as localized disease when patients presented with primary GIST without metastases and without indication for neoadjuvant treatment. Locally advanced disease was defined as patients who presented with primary GIST without metastases with an indication for neoadjuvant treatment. Comorbidities were scored using the Charlson Comorbidity Index (CCI) [22].

2.3 Categories of Treatment Adjustment

Per treatment line data were collected from first initiation of therapy at the starting dose to date of first adjustment of treatment. Reasons for first adjustment were divided into planned end of treatment due to fixed time of (neo) adjuvant treatment or in a palliative setting when limited

metastases could still be resected after treatment, an adverse event associated with TKIs, dose modification, progressive disease, or other reasons (e.g. [surgery for] other comorbidities, wishes of the patient, death due to other causes, end of study treatment, or no metabolic response on positron emission tomography [PET] imaging). Adverse events associated with TKIs were scored using the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. Dose modification was defined as adjusting the dose based on KIT exon 9 mutation or on measured trough plasma concentrations. Dose reduction was defined as a reduction in dose compared with the starting dose per specific treatment line; dose escalation was defined as an increase in dose compared with the starting dose; and dose interruption was defined as a period of interruption of a TKI followed by restarting that TKI at the same dose. Starting doses of 400 mg once daily for imatinib, 37.5 mg once daily continuous for sunitinib, and 160 mg once daily (3 weeks on and 1 week off) for regorafenib were considered standard doses. According to the Dutch GIST standard-of-care guideline, both sunitinib at a continuous dosage of 37.5 mg/day and sunitinib at an intermitting dosage of 50 mg/day (4 weeks on, 2 weeks off) can be administered as the standard dosage. From a practical and pharmacological point of view, there is a strong preference for the continuous schedule, therefore 37.5 mg is defined as the standard dose in this study.

2.4 Imatinib Trough Plasma Calculations

Due to the linear elimination of imatinib, trough plasma concentrations were calculated using the following algorithm: $C_{trough} = C_{measured} * 0.5^{(T_{dosinginterval} - TAD/t_{½})}$ [23]. To calculate the time after dosing (TAD), the time of blood withdrawal was subtracted from the time of the last dosing event. If the blood withdrawal was taken before the time to peak drug concentration (T_{max}), the imatinib trough plasma concentrations could not be calculated. The time of dosing interval ($T_{dosinginterval}$) and TAD are reported in hours. The elimination half-life ($t_{½}$) for imatinib is 18 h.

Imatinib trough plasma concentrations were measured in nanograms per liter (ng/mL), considering 1100–3200 ng/mL as the therapeutic range.

All imatinib trough plasma concentrations of blood withdrawals taken during outpatient clinic visits and calculated by pharmacists and/or related to studies from 1 week after initiation of imatinib until a maximum of 1 year of treatment with imatinib were collected. For imatinib trough plasma concentrations, the medians of all measured plasma concentrations per patient were used in a predefined time period (3 months vs. 1 year after the initiation of imatinib). The time period was defined as the start of treatment to the first adjustment or planned end of treatment or time of last FU in the case of ongoing treatment with imatinib at the time of data extraction (at data cut-off [DCO]).

2.5 Overall Survival Analysis by Dose Reduction

To compare OS in patients with and without dose reduction in different treatment lines, only patients with treatment in a palliative setting were included. Patients treated with imatinib or sunitinib in a (neo)adjuvant setting were excluded from this analysis.

2.6 Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. Patients were divided into two age groups; younger patients (age <70 years) and older patients (≥70 years) [24–26].

Absolute numbers and percentages within both age groups were reported for categorical and dichotomous variables. For continuous variables, mean and standard deviation (SD) were reported in the case of normally distributed data, and median and interquartile range (IQR) were reported for non-normally distributed data. Baseline characteristics were compared using the Chi-square test (for nominal variables) or the Mann–Whitney test (for ordinal variables). The Mann–Whitney test was also used to compare differences in the reason for first adjustment of treatment (adverse event, dose modification, progressive disease, or other reasons) per age group. To compare the median of all imatinib trough plasma concentrations per patient per age group taken within 3 months and within 1 year after the start of treatment, the Mann–Whitney test was used. The association of dose reduction and OS was analyzed using the landmark approach [27]. In our study, a landmark time of 3 months was chosen. Only patients who were alive and still in FU at the landmark time (with a minimum FU of ≥3 months) were included in this analysis. At the landmark time, patients were classified as patients with dose reduction in case they underwent a dose reduction within 3 months from initiation of a TKI in a palliative setting. All statistical analyses were performed using both IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA) and the statistical program R version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) [28, 29]. *P*-values ≤0.05 were considered statistically significant.

3 Results

3.1 Study Population

In this cohort, a total of 871 patients with GIST treated with a TKI were included and 581 patients were excluded due to no treatment with a selected TKI or lost to FU. The younger

(<70 years) and older (≥70 years) age groups comprised 577 and 294 patients, respectively (Fig. 1). Baseline characteristics by age group are presented in Table 1.

Younger patients more often had a non-gastric primary GIST, especially located in the small bowel, while older patients had more comorbidities compared with younger patients. Primary tumor size, disease stage at presentation and mutation status did not differ between both age groups (Table 1).

3.2 Dosing Patterns in Treatment with Tyrosine Kinase Inhibitors (TKIs), by Age Group

Dosing patterns for starting doses in all treatment lines are shown in Table 2. Two patients were not treated with imatinib as the first treatment line due to comorbidity of a renal cell carcinoma and participation in a clinical trial. Almost all patients in both age groups started at the standard dose of 400 mg once daily. In most patients in whom treatment with imatinib was started in a higher dose, this was due to KIT exon 9 mutations (7/13 younger patients and 4/5 older patients). In contrast to treatment with imatinib, treatments with sunitinib and regorafenib were more often started in a reduced dose, especially in older patients. Older patients treated with sunitinib significantly started at a lower dose compared with younger patients who started more frequently with a higher dose ($p < 0.001$) (Table 2).

3.3 Treatment Setting and Ongoing Treatment at Time of Data Cut-Off

In this study, sunitinib and regorafenib were mostly started in a palliative setting for both age groups. For imatinib, this was only approximately 40%; the other patients were treated in the (neo)adjuvant setting (Table 3).

At the time of DCO, 66 (11.5%) younger patients and 37 (12.6%) older patients were receiving active treatment with imatinib, 11 (7%) younger patients and 3 (5%) older patients were receiving active treatment with sunitinib, and 5 (8%) younger and no older patients were receiving active treatment with regorafenib at the time of DCO.

3.4 Planned End of Treatment After Starting on a Standard Dose

A total of 486 younger and 241 older patients had ended or adjusted treatment with imatinib after starting on a standard dose (400 mg/day). In treatment with (neo)adjuvant imatinib or in a palliative setting with indication for resection of metastasis, 147 (30.2%) younger and 56 (23.2%) older patients completed treatment after starting on a standard dose (= planned end of treatment) without any adjustments.

A total of 82 younger and 29 older patients had ended or adjusted treatment with sunitinib after starting on a standard dose (37.5 mg/day). In treatment with sunitinib started at a

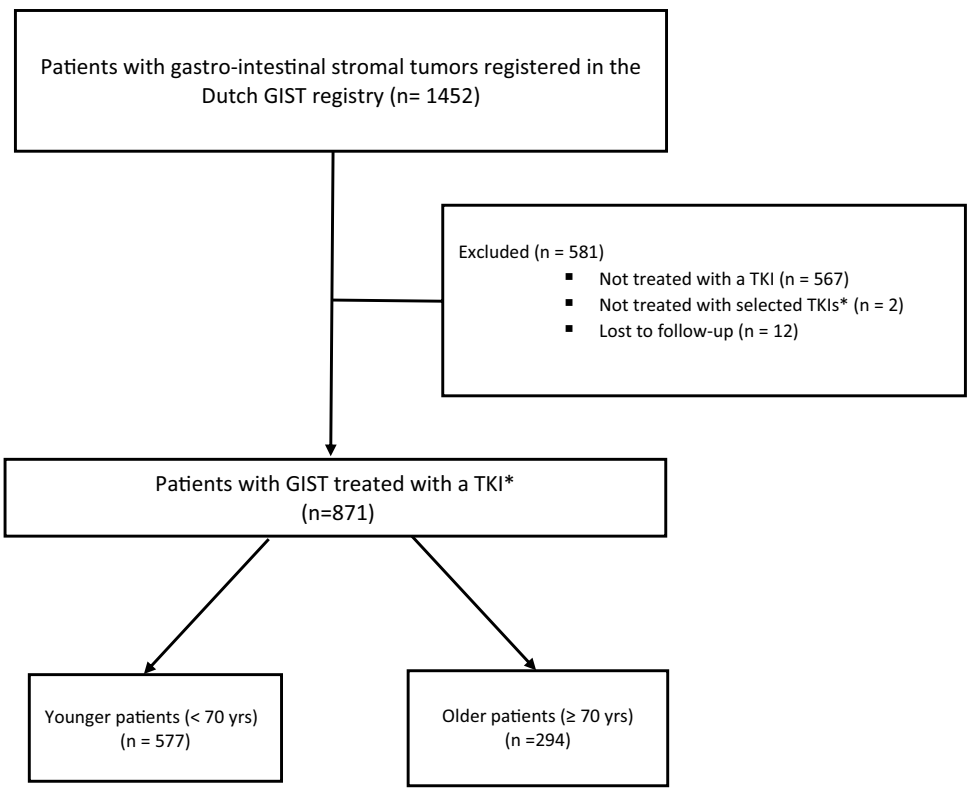

Fig. 1 Patient selection process. [a]Imatinib, sunitinib and regorafenib. *GIST* gastrointestinal stromal tumors, *TKI* tyrosine kinase inhibitor

Table 1 Baseline patient characteristics of GIST patients treated with TKIs, by age group

	Total [$n = 871$]	Younger patients [$n = 577$]	Older patients [$n = 294$]	p-Value[a]
Age[b] [median (IQR)]	64 (55–72)	59 (51–64)	75 (72–79)	
Sex				
Male	500 (57.4)	344 (59.6)	156 (53.1)	0.070
Female	371 (42.6)	233 (40.4)	138 (46.9)	
Missing	*0*	*0*	*0*	
Primary location				
Gastric	452 (51.9)	278 (48.2)	174 (59.2)	0.004[a]
Small bowel	219 (25.1)	163 (28.2)	56 (19.0)	
Duodenal	57 (6.5)	43 (7.5)	14 (4.8)	
Colon	15 (1.7)	8 (1.4)	7 (2.4)	
Rectum	67 (7.7)	48 (8.3)	19 (6.5)	
Esophagus	11 (1.3)	5 (0.9)	6 (2.0)	
Other	50 (5.7)	32 (5.6)	18 (6.1)	
Missing	*0*	*0*	*0*	
Baseline tumor size, cm				
≤2	12 (1.5)	10 (1.8)	2 (0.7)	0.306
>2 ≤ 5	135 (16.5)	81 (14.9)	54 (19.5)	
>5 ≤ 10	271 (33.0)	181 (33.3)	90 (32.5)	
>10	402 (49.0)	271 (49.9)	131 (47.3)	
Missing	*51*	*34*	*17*	
Size, mm [median (IQR)]	96 (60–140)	99 (60–140)	91 (55–140)	
Presentation at registry				
Localized	226 (25.9)	154 (26.7)	72 (24.5)	0.862
Locally advanced	310 (35.6)	200 (34.7)	110 (37.4)	
Metastasized	313 (35.9)	207 (35.9)	106 (36.1)	
Multiple primary locations	22 (2.5)	16 (2.8)	6 (2.0)	
Missing	*0*	*0*	*0*	
Mutation				
KIT	671 (83.3)	448 (82.5)	223 (84.8)	0.329
Exon 11	567	375	192	
Exon 13	13	10	3	
Exon 17	6	4	2	
Exon 9	80	55	25	
Missing	*5*	*4*	*1*	
PDGFRA	61 (7.6)	38 (7.0)	23 (8.7)	
Wild-type	74 (9.2)	57 (10.5)	17 (6.5)	
Missing	*65*	*34*	*31*	
CCI score				
≤2	737 (84.6)	512 (88.7)	225 (76.5)	<0.001[a]
3–5	106 (12.2)	52 (9.0)	54 (18.4)	
≥6	28 (3.2)	13 (2.3)	15 (5.1)	
Missing	*0*	*0*	*0*	

Data are expressed as *n* (%) unless otherwise specified

GIST gastrointestinal stromal tumor, *TKIs* tyrosine kinase inhibitors, *IQR* interquartile range, *KIT* receptor tyrosine kinase, *PDGFRA* platelet-derived growth factor receptor, *CCI* Charlson comorbidity Index

[a]A p-value <0.05 indicates significance (Chi-square for nominal variables and Mann–Whitney for ordinal variables) across categories

[b]Age at diagnosis

Table 2 Dosing patterns for starting doses in all treatment lines in both age groups

	Younger patients	Older patients	*p* value
Treatment with imatinib ($n = 869$)[b]	576	293	0.311
Standard dose (400 mg)	550 (95.7)	278 (95.2)	
Lower starting dose	12 (2.1)	9 (3.1)	
Higher starting dose	13 (2.3)	5 (5.1)	
Treatment with sunitinib ($n = 213$)[b]	155	58	<0.001[a]
Standard dose (37.5 mg)	89 (58.9)	31 (53.4)	
Lower starting dose	9 (6.0)	18 (31.0)	
Higher starting dose	53 (35.1)	9 (15.5)	
Treatment with regorafenib ($n = 92$)[b]	76	16	0.345
Standard dose (160 mg)	55 (76.4)	10 (62.5)	
Lower starting dose	17 (23.6)	6 (37.5)	

Data are expressed as *n* (%)

[a]A *p*-value <0.05 indicates significance (Chi-square for nominal variables and Mann-Whitney for ordinal variables) across categories between age groups

[b]$N = 2$ patients with missing data for the imatinib starting dose, $n = 4$ (younger) patients for sunitinib and $n = 4$ (younger) patients for regorafenib

Table 3 Treatment setting per age group (all starting doses)

Treatment setting	Younger patients	Older patients
Imatinib	576	293
Neoadjuvant	219 (38)	129 (44)
Adjuvant	127 (22)	40 (13.7)
Palliative	230 (39.9)	124 (42.3)
Sunitinib	155	58
Neoadjuvant	10 (6.5)	5 (8.6)
Adjuvant	1 (0.6)	0
Palliative	144 (92.9)	53 (91.5)
Regorafenib		
Palliative	76	16

standard dose, 1 (1.2%) younger patient completed neoadjuvant treatment (= planned end of treatment) without any adjustment.

3.5 Reasons for First Adjustment Treatment

The main reason for first adjustment of treatment with imatinib after starting on a standard dose in older patients was an adverse event (19.5% [95/486] of younger patients vs. 45.6% [110/241] of older patients) (Table 4). In younger patients, other reasons for treatment adjustment were more frequent ($p \leq 0.001$) (Table 4): dose modification based on trough plasma concentrations (21.8% [106/486] of younger patients vs. 11.2% [27/241] of older patients) or progressive disease (23.0% [112/486] of younger patients vs. 16.2% [39/241] of older patients). The median time to first adjustment of treatment with imatinib at a standard dose was 4 (1–15) months in younger patients compared with 2 (1–11) months in older patients (Table 4).

Table 4 First adjustment in treatment with imatinib after starting on a standard dose

	Younger patients [$n = 486$][a]	Older patients [$n = 241$][a]	*p*-Value
First adjustment [*n* (%)]			
Adverse event	95 (19.5)	110 (45.6)	<0.001
Dose modification	106 (21.8)	27 (11.2)	
Progressive disease	112 (23.0)	39 (16.2)	
Other[a]	26 (5.3)	9 (3.7)	
Median time to first adjustment, in months [median (IQR)]	4 (1–15)	2 (1–11)	

Data are expressed as *n* (%) unless otherwise specified

IQR interquartile range, *PET* positron emission tomography

[a]Overall, 147 (30.2%) younger patients and 56 (23.2%) older patients completed treatment after starting on a standard dose (= planned end of treatment) and were subsequently excluded from this table and the statistical analysis (Mann–Whitney test). Other reasons for first adjustment in treatment were (surgery for) other comorbidities, wishes of the patient, death due to other causes, or no metabolic response on PET imaging

Similar to treatment with imatinib, older patients ($n = 17$ [58.6%]) treated with sunitinib at a standard dose more often had an adjustment of treatment due to adverse events compared with younger patients ($n = 35$ [42.7%]; $p = 0.22$) (Online Resource Table S1). The median time to first adjustment of treatment with sunitinib at a standard dose was shorter compared with imatinib in both age groups (2 months [1–5.5] in younger patients compared with 1 month

[0–3.5] in older patients). Similarly, in treatment with regorafenib at the starting dose (all doses), both age groups most often had treatment adjusted due to adverse events (40 [56.3%] younger patients and 13 [81.3%] older patients). Progressive disease was another common reason for first adjustment of treatment with regorafenib in 27 (38.0%) younger patients versus 3 (18.8%) older patients ($p = 0.07$) [Online Resource Table S2]. Median time to first adjustment of treatment with regorafenib in younger patients was 1 month (0–5), and 0.5 months (0–3.75) in older patients.

3.6 Dosing Patterns After Treatment Adjustment Due to an Adverse Event

Adjustment of imatinib after starting on a standard dose because of an adverse event most often resulted in dose reduction in both age groups (42.1% of younger patients vs. 48.2% of older patients) (Fig. 2). Imatinib was permanently discontinued (= end of treatment) in a larger percentage of younger patients (31.6% of younger patients vs. 24.5% of older patients) (Fig. 2). Similar to treatment with imatinib, adverse event as the reason for first adjustment of treatment with sunitinib after starting on a standard dose was followed by dose reduction in most patients in both age groups (62.9% younger patients vs. 64.7% older patients) (Online Resource Fig. S1). In addition, younger patients more often underwent dose interruption, while older patients more often permanently discontinued treatment with sunitinib (Online Resource Fig. S1). Adjustment of regorafenib after the starting dose (in all doses) because of an adverse event was also most often followed by dose reduction in both age groups (85.0% younger patients vs. 53.8% older patients). In most other older patients (5 [38.5%]), this resulted in permanent discontinuation of treatment with regorafenib.

3.7 Adverse Events as Reasons for Adjustment of Treatment, by Age Group

The most common adverse events leading to adjustment of imatinib in both age groups were nausea, skin toxicity and fatigue. In younger patients, skin toxicity (15.8% [15/95]) was most frequently registered as the reason for adjustment of treatment with imatinib after starting on a standard dose, while in older patients, nausea (19.1% [21/110]) and fatigue (14.5% [16/110] were most frequent (Fig. 3). Periorbital edema and edema were also common adverse events leading to adjustment of imatinib treatment in both age groups. Median time to first adjustment of imatinib at a standard dose due to adverse events was 3 months (1–8) in younger patients and 2 months (0–3.5) in older patients.

The most common adverse events leading to adjustment of treatment with sunitinib after starting on a standard dose in younger patients were palmar-plantar erythrodysesthesia (17.1% [6/35]), diarrhea (14.3% [5/35]) and mucositis (11.4% [4/35]). In older patients, these were fatigue (23.5% [4/17]), palmar-plantar erythrodysesthesia (17.6% [3/17])

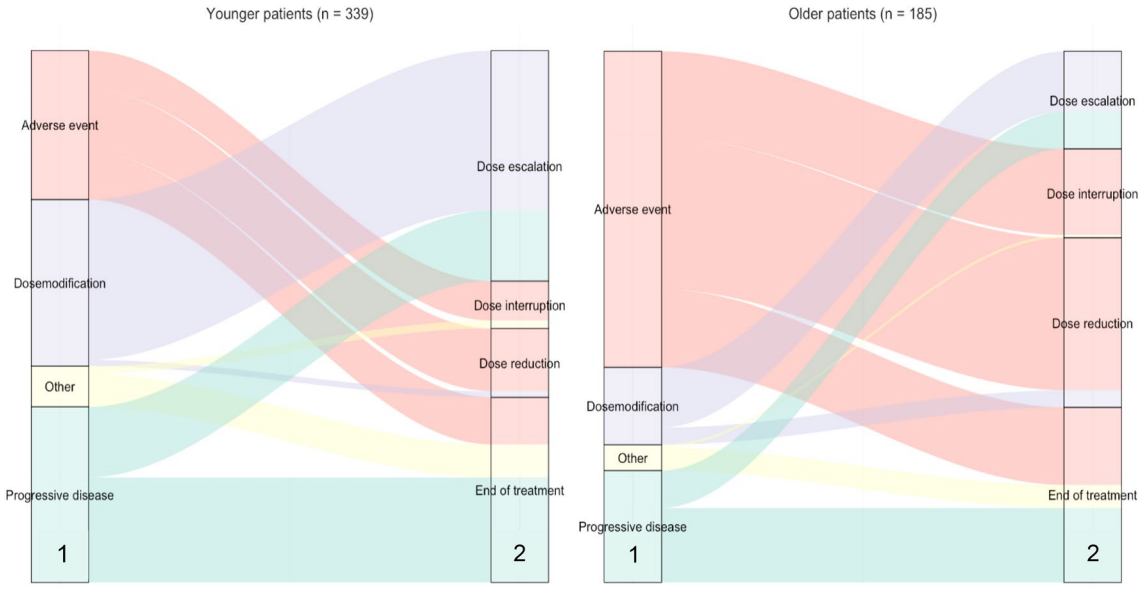

Fig. 2 Dosing patterns after imatinib treatment adjustment. The reasons for first adjustment (1) of treatment with imatinib after starting on the standard dose, followed by the next treatment step (2) for both younger and older patients are shown. This figure represents proportions; absolute numbers differ in both groups. Only patients who started treatment on a standard dose were included. Other reasons for first adjustment in treatment were (surgery for) other comorbidities, wishes of the patient, death due to other causes, or no metabolic response on PET imaging. *PET* positron emission tomography

and diarrhea (11.8% [2/17]) [Online Resource Fig. S2]. Median time to first adjustment of sunitinib at a standard dose due to adverse events was 1 month (0–2) in younger patients and 0 months (0–1.5) in older patients.

The most common adverse events as the reason for adjustment of treatment with regorafenib after starting on a standard dose in both age groups were palmar-plantar erythrodysesthesia (34.3% [12/35] of younger patients vs. 25.0% [2/8] of older patients), fatigue (17.1% [6/35] of younger patients vs. 37.5% [3/8] of older patients) and skin toxicity (11.4% [4/35] of younger patients vs. 12.5% [1/8] of older patients) (Online Resource Fig. S3).

3.8 Imatinib Trough Plasma Concentrations, by Age Group

Of all patients treated with imatinib with the standard dose of 400 mg once daily, at least one trough plasma concentration was determined within 1 year after the start of treatment in 36.2% (199/550) of younger patients and 34.2% (95/278) of older patients. In younger and older patients, a total of 515 and 235, respectively, imatinib trough plasma concentrations were measured. In both age groups, a median of 2 (IQR 1–4), with a range of 1–9, trough plasma concentrations per patient were measured within 1 year after the start of imatinib. Median trough plasma concentrations were higher in older patients (1228 ng/mL [IQR 959–1687]) compared with younger patients (1035 ng/mL [IQR 773–1377]; $p < 0.001$).

Within the first 3 months after the start of treatment with imatinib, trough plasma concentrations were measured in 169 younger patients ($n = 280$) and 84 older patients ($n = 140$). Within this timeframe, older patients also had higher median trough plasma concentrations (1308 ng/mL [IQR 1013–1740]) than younger patients (1080 ng/mL [IQR 779–1524]; $p = 0.003$).

3.9 Oncological Outcome Related to Dose Reduction of Treatment with TKIs

With a landmark time of 3 months after initiation of imatinib in a palliative setting, a total of 321/355 patients survived and were included in the analysis. A total of 34 patients were excluded; 11 patients died and 4 patients wished to stop treatment within 3 months after initiation

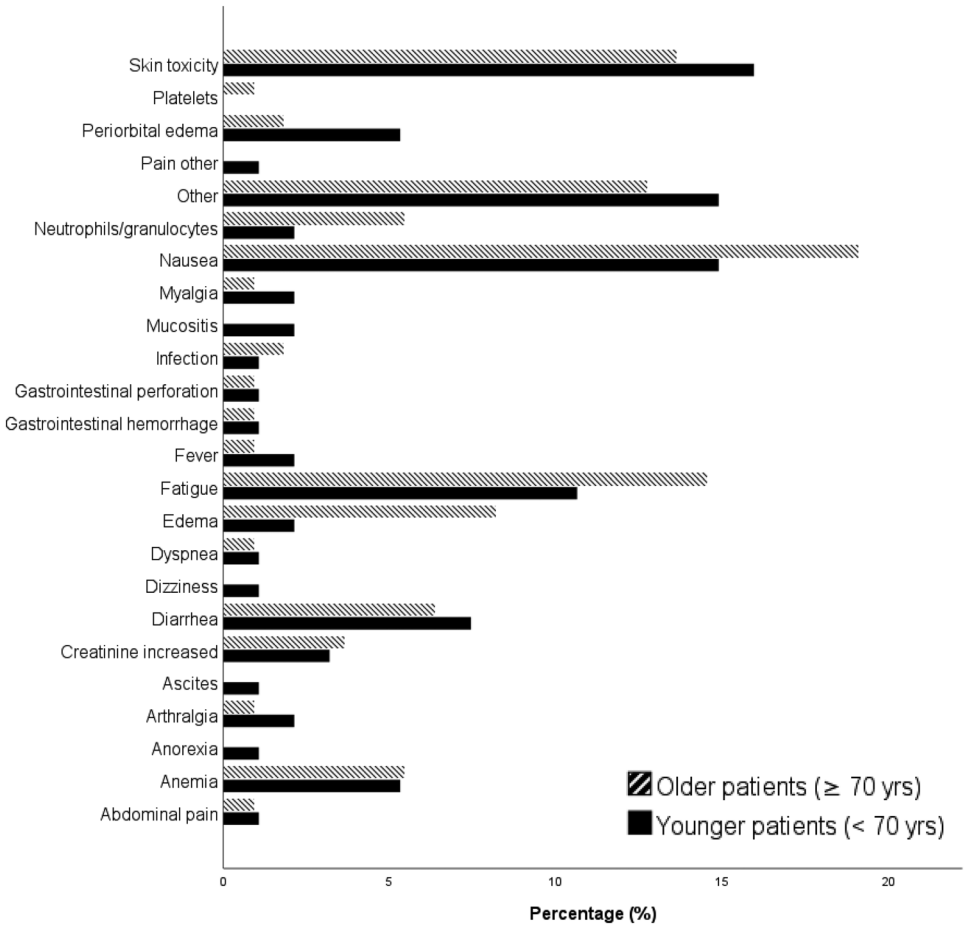

Fig. 3 Adverse events as the reason for first adjustment of treatment with imatinib. This figure only shows patients who had an adverse event as the reason for first adjustment of treatment with imatinib (starting on a standard dose): 95 younger patients and 110 older patients were included. Other adverse events included bleeding ($n = 1$), anemia ($n = 1$), pneumonitis ($n = 3$), liver toxicity ($n = 6$), bone pain ($n = 1$), headache ($n = 3$), dyspnea ($n = 4$), pulmonary edema ($n = 1$), dizziness ($n = 1$), erectile dysfunction ($n = 1$), hypokalemia ($n = 1$), malaise ($n = 2$), hair loss ($n = 1$), pruritis ($n = 2$), coldness ($n = 1$), and unknown ($n = 1$).

of imatinib, while 19 patients had not yet reached the 3-month FU period at DCO. A total of 35/321 (10.9%) patients had a dose reduction within 3 months after initiation of imatinib. The 1-year survival rate was 92.9% (CI 89.9–96.1) without dose reduction and 83.4% for patients with a dose reduction (CI 71.0–98.0; $p = 0.207$) [Online Resource Fig. S4].

With a landmark time of 3 months after initiation of sunitinib in a palliative setting, a total of 160/197 patients survived and were included, whereas 49 (30.6%) patients had a dose reduction 3 months after initiation of sunitinib. Of the 37 excluded patients, 23 patients died, 1 patient was referred to the general practitioner for best supportive care, 2 patients were followed at another hospital, and 1 patient wished to stop treatment within 3 months after initiation of sunitinib. A total of 10 patients had not yet reached the 3-month FU period at the DCO. The 1-year survival rate was 69.7% (CI 61.3–79.2) without dose reduction and 69.2% for patients with a dose reduction (CI 56.9–84.1; $p = 0.547$) (Online Resource Fig. S5).

With a landmark time of 3 months after initiation of regorafenib, a total of 71/92 patients survived and were included, whereas 31 (43.7%) patients had a dose reduction 3 months after initiation of regorafenib. Of the 21 excluded patients, 12 patients died and 4 patients were referred to the general practitioner for best supportive care within 3 months after initiation of regorafenib. A total of five patients had not yet reached the 3-month FU period at DCO. The 1-year survival rate was 52.5% (CI 38.4–71.8) without dose reduction and 61.3% for patients with a dose reduction (CI 46.3–81.1; $p = 0.784$) (Online Resource Fig. S6).

4 Discussion

This large multicenter study shows that older patients with GIST treated with a TKI most often had adverse events as the reason for first adjustment of treatment in all treatment lines. This was especially the case for treatment with imatinib. Older patients appeared to adjust treatment earlier due to adverse events compared with younger patients. For patients treated with sunitinib and regorafenib, these differences were not found, which could be explained by the clinical decision to only treat fit older patients, with less comorbidities, with these later line treatments.

If the reason for first dose adjustment of imatinib (started at the standard dose) was an adverse event, this was mainly followed by dose reduction in older patients, while in younger patients treatment was more often permanently discontinued. This could be explained by the fact that younger patients qualify for invasive treatment options such as surgery and are more often eligible for treatment with second and third treatment lines that are not prescribed to older patients because of a higher risk of adverse events. The latter can also explain the observation that younger patients more often had dose interruptions for sunitinib, while older patients more often permanently discontinued treatment.

The occurrence of adverse events as the reason for treatment adjustment differed between both age groups. In older patients, adverse events such as fatigue and nausea were most often registered as reasons of adjustment, while in younger patients, this was skin toxicity. This difference in presentation of adverse events between different age groups could be explained by general adverse events, such as fatigue and nausea, that are more common in patients with comorbidity or with co-medication, which is more often seen in older patients. However, in this heterogenous group of older patients, important factors such as frailty, polypharmacy, cognitive impairments, nutritional status and other geriatric problems, which may also influence the safety and tolerability of treatment, have not been taken into account. In addition, due to the retrospective design and small sample sizes in presentation of different adverse events, no formal statistical evaluation could be performed. Older patients showed significantly higher median imatinib trough plasma concentrations compared with younger patients, which was similar to the findings of Italiano et al., who concluded that imatinib trough plasma concentrations increased with age [30]. Despite higher trough plasma concentrations in older patients, previous studies have not shown significant differences between younger versus older patients [24, 30]. In these studies, only one plasma sample per patient at steady state was collected, but time from initiation of imatinib to withdrawal of the plasma sample varied per patient. As the half-life time of imatinib is 18 h, steady state should be reached within 2.5–3.5 days. Due to high intra- and inter-individual variability, the best choice for monitoring imatinib plasma concentrations would be to administer imatinib at a constant dose for a set period of time [31]. Therefore, in this study, we collected all measured imatinib plasma concentrations from initiation of imatinib at a standard dose of 400 mg until 1 year after the start of treatment.

Within the first 3 months after the start of treatment with imatinib, older patients showed higher trough plasma concentrations compared with younger patients and also more often had adverse events as the reason for first adjustment of treatment with imatinib followed by dose reduction. Nevertheless, OS in patients with or without dose reduction did not significantly differ. Over time, a decreasing trend of median trough plasma concentrations was seen in both age groups. In previous research, this phenomenon of lowered trough plasma levels over time, potentially causing disease progression, is known as ‘acquired pharmacokinetic drug resistance’

[16, 32]. However, in older patients, median imatinib trough plasma concentrations within 1 year remained well above the therapeutic level. Therefore, a lower starting dose followed by dosing adapted to trough plasma concentrations ensuring adequate systemic exposure could be considered in older patients. This might avoid early adverse events in older patients and preserve effective trough plasma concentrations over time.

The retrospective design of this analysis results in patients with missing data, which could introduce selection bias. Another limitation of this study is that we could not perform disease-specific survival analyses to investigate the impact of lower starting doses on oncological outcomes. Furthermore, the survival analysis did not include other prognostic factors as covariates affecting survival. Nevertheless, this analysis was most suitable to limit immortal time bias. The relationship between dosing and oncological outcome could be biased due to disease-related conditions, leading to both lower dosing and worse survival. Further prospective research is needed to optimize dosing patterns in different age groups while taking frailty status and drug interactions [31] in especially older patients into account. There is a large heterogeneity between fit and non-fit older patients, where patients older than 70 years with cancer are most often non-fit, reflected by high frailty scores [20]. In this patient group, lower doses of TKIs, leading to a lower risk of adverse events, might be accepted, even if leading to lower effectivity in terms of (progression-free) survival. Other relevant endpoints in older patients, such as self-sufficiency and quality of life, should also be taken into account. This study could not collect imatinib trough plasma concentration data for all patients since the measurement of trough plasma concentrations was first implemented into the Dutch guidelines from 2010. Nevertheless, this multicenter study is the largest series based on real-life data examining dosing patterns in different age groups of patients with GIST treated with TKIs, taking trough plasma levels into account as a foundation for further prospective research.

5 Conclusion

Older patients showed higher trough plasma concentrations compared with younger patients, and also more often had adverse events as the reason for first adjustment of treatment with imatinib followed by dose reduction. However, in a landmark analysis, patients with imatinib dose reductions had no poorer outcomes compared with patients not requiring a dose reduction.

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Declarations

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Ethics Approval This study was approved by local review boards of centers participating in the DGR.

Consent to Participate Not applicable.

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Data Availability Statement All data generated or analyzed during this study are included in this published article.

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Author Contributions RFB: Conceptualization, methodology, formal analysis, investigation, data curation, writing – original draft. KEB: Conceptualization, methodology, validation, formal analysis, investigation, writing – review and editing, supervision. ER: Data curation, writing – review and editing. MM: Data curation, writing – review and editing. IMED: Writing – review and editing. HG: Writing – review and editing. RHJM: Writing – review and editing. NS: Writing – review and editing. PdG: Conceptualization, methodology, validation, formal analysis, writing – review and editing, supervision. AKLR: Conceptualization, methodology, validation, formal analysis, writing – review and editing, supervision

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