Improving diagnosis and treatment of gastrointestinal stromal tumor (GIST) patients: Results from the Dutch GIST Registry

Farag-Kal, S.

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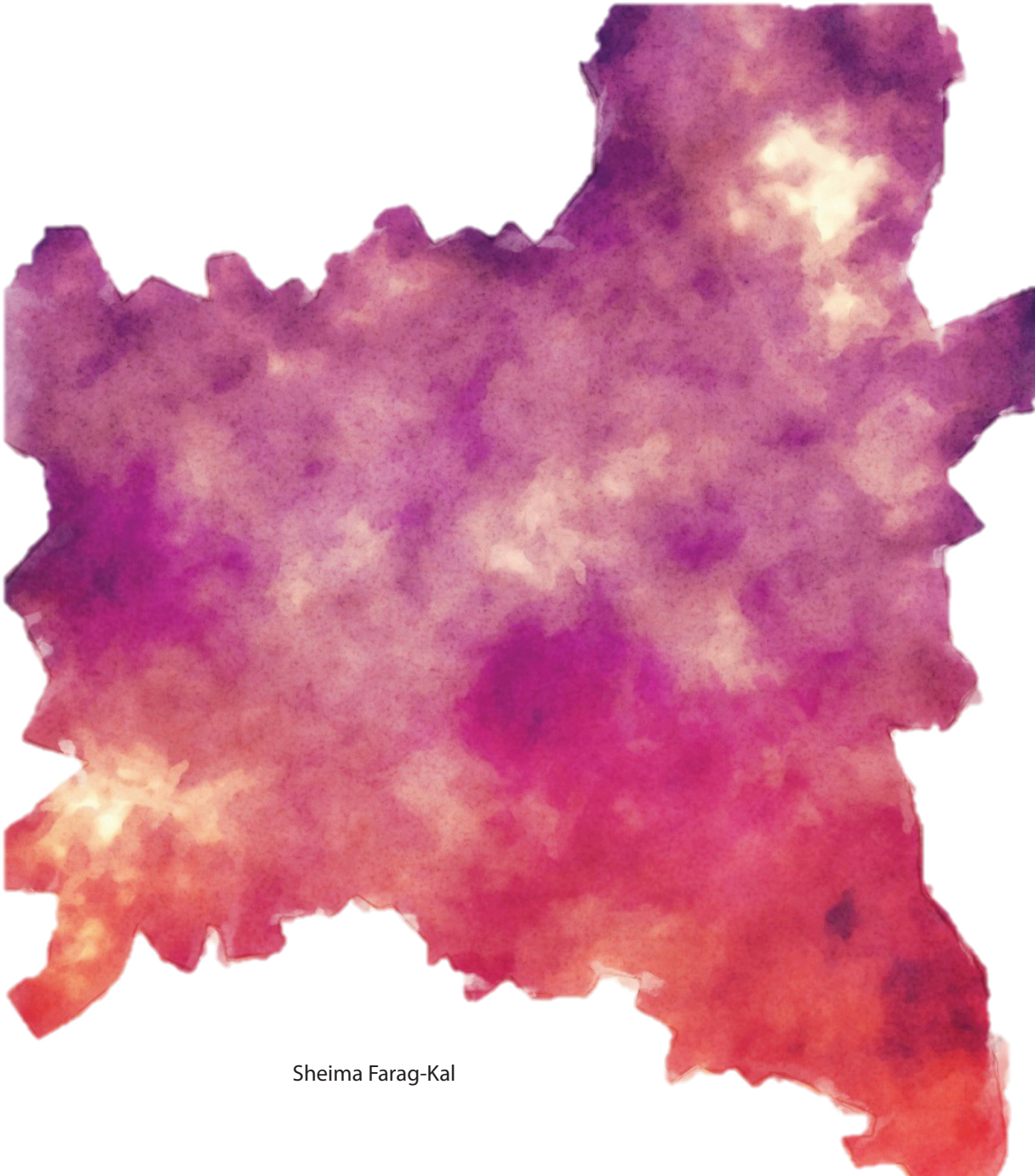

Sheima Farag-Kal

Improving diagnosis and treatment of gastrointestinal stromal tumor (GIST) patients

Results from the Dutch GIST Registry

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PhD thesis, Leiden University, The Netherlands

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"If you don't like something, change it. If you can't change it, change your attitude"
Maya Angelou, 1928-2014

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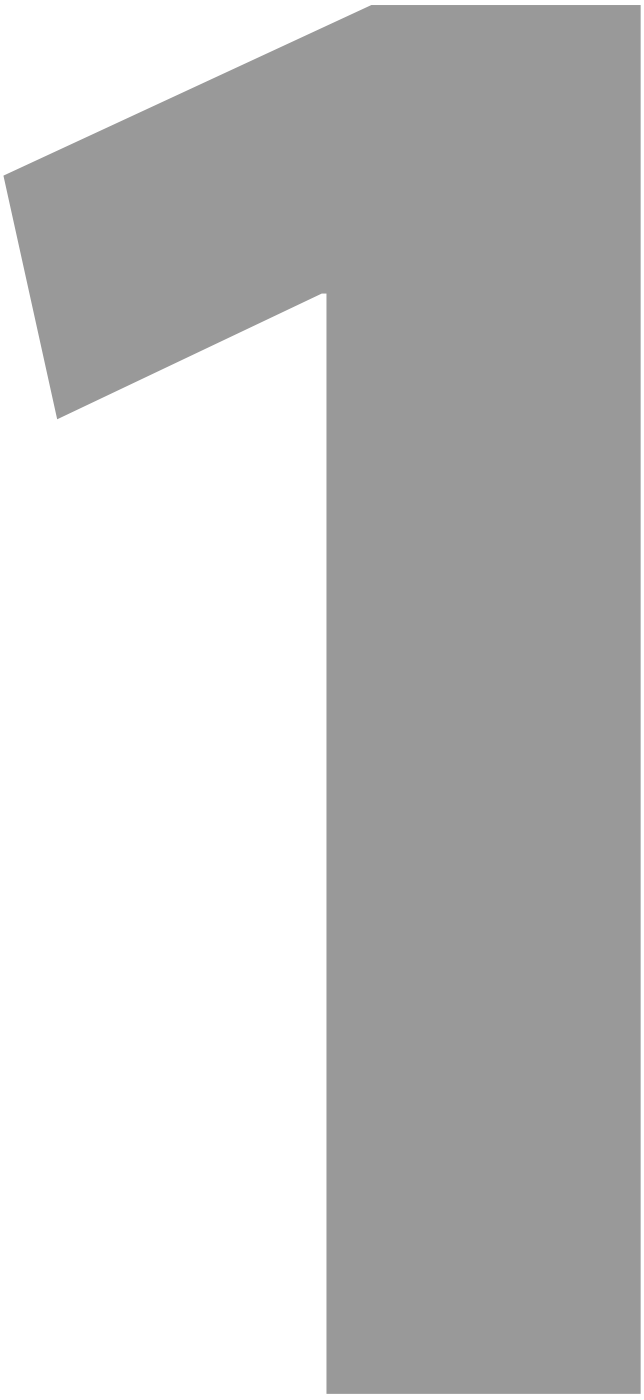

Chapter 1

General introduction and thesis outline

General Introduction

GIST diagnosis and pathogenesis

Gastrointestinal stromal tumor (GIST) is a rare mesenchymal malignancy in the gastrointestinal tract and arises from the interstitial cells of Cajal.(1) GIST can occur anywhere in the gastrointestinal tract, but predominantly arises in the stomach (60%) and small intestine (25%).(1) Worldwide, the annual incidence is between 11 and 19.6 per million. In the Netherlands the incidence is estimated at 250 patients per year. The highest incidence is found in the age group of 60-74 years. Clinical symptoms are mostly nonspecific and involve satiety, dysphagia, fatigue, abdominal pain, and obstruction.(2) Anemia is often revealed during workup and is mostly related to intratumoral hemorrhage or mucosal bleeding. However, GIST can also be detected in asymptomatic patients during diagnostics for other purposes.

In 1998 Hirota et al. published their discovery about the expression of KIT (CD117) in over 95% of GISTs.(3) They found that an activating mutation involving the *KIT* gene is important to their tumorigenesis. KIT is a type III tyrosine kinase receptor (TKR) and binding of stem cell factor (SCF) (the ligand of KIT) results in homodimerization and kinase activation. An oncogenic mutation in *KIT* causes ligand-independent activation. In 75% of GISTs an activating mutation in *KIT* is found and in 10% an activating mutation involving the platelet-derived growth factor receptor alpha (*PDGFRA*), another type III TKR,is found. Over 65% of GISTs harbor a mutation in *KIT* exon 11, in the juxtamembrane domain. *PDGFRA* mutations mostly involve exon 18, in the activation loop.(1) (Figure 1)

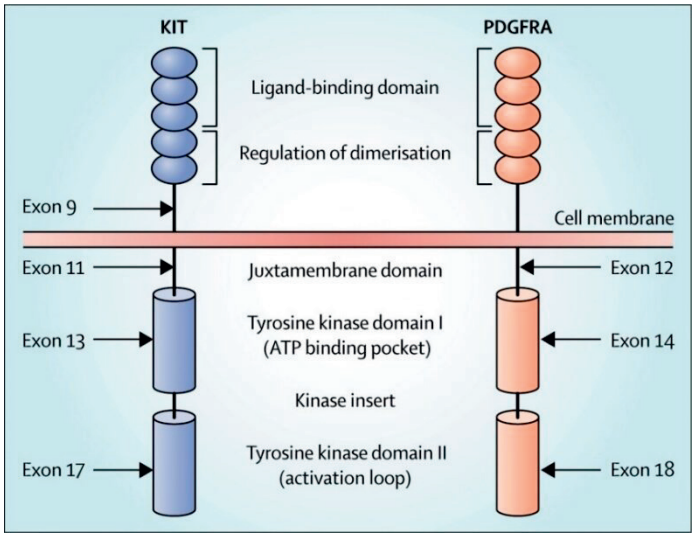

Figure 1: Structure of KIT and PDGFRA receptor kinases. *Adapted from Joensuu, Hohenberger, and Corless 2013* [7].

Approximately 15% of all GISTs are wild type for *PDGFRA* and *KIT*. This is a heterogeneous group and includes succinate dehydrogenase subunit (SDH)-deficient GISTs, neurofibromatosis type 1 (NF1) associated GISTs, and BRAF/RAS mutated GISTs.(4) SDH-deficient GISTs and NF1 associated GISTs can be related to familial syndromes. The Carney-Stratakis syndrome involves germline mutations of SDHA, -B, -C, and –D germline mutations leading to a dyad of GIST and paraganglioma.(5) The Carney triad on the other hand is found in non-familiar SDHB-deficient GISTs and involves gastric GIST, paraganglioma, and pulmonary chondroma.(5) Familial GISTs involving germline *KIT*- or *PDGFRA*-mutations are very rare and are associated with multiple and young onset GISTs.(6)

Treatment of GIST

Primary treatment of GIST consists of resection of the tumor. The aim of surgery is complete resection (R0) of the GIST without dissection of lymph nodes.(8) Despite surgery disease recurrence is seen in approximately 40% within 5 years.(9) Tumor site, mitotic count, and tumor size are important prognostic factors for recurrence.(10) In general, tumors originating from a non-gastric site have more malignant potential than gastric GISTs and larger tumors and tumors with high mitotic count are more likely to recur. In large tumors a laparoscopic approach is discouraged, because of the high risk of tumor rupture associated with high risk of recurrence. Table 1 shows the risk stratification as defined by the Armed Forces Institute of Pathology (AFIP). (Table 1) This stratification method is supported by 3 large retrospective studies on prognostic determinants of GIST. (10–12)

Table 1: Risk classification for primary GIST by mitotic index, size, and tumor site. *Adapted from Miettinen and Lasota 2006*.

Tumor Parameters		**Tumor Location**			
Tumor Size	**Mitotic Rate**	**Gastric**	**Jejunal and Ileal**	**Duodenal**	**Rectal**
≤2 cm	≤5/50 HPFs	0% None	0% None	0% None	0% None
>2 cm ≤5 cm	≤5/50 HPFs	1.9% Low	4.3% Low	8.3% Low	8.5% Low
>5 cm ≤10 cm	≤5/50 HPFs	3.6% Low	24% Moderate	34% High‡	57% High‡
>10 cm	≤5/50 HPFs	12% Moderate	52% High		
≤2 cm	>5/50 HPFs	0%†	50%†	§	54% High
>2 cm ≤5 cm	>5/50 HPFs	16% Moderate	73% High	50% High	52% High
>5 cm ≤10 cm	>5/50 HPFs	55% High	85% High	86% High	71% High‡
>10 cm	>5/50 HPFs	86% High	90% High		

† Tumor categories with very few cases; ‡ Combined in duodenal and rectal GISTs because of small number of cases; § No tumor of such category included in the study.

In 2002 the drug imatinib was introduced in the treatment of GIST. This is a tyrosine kinase inhibitor (TKI) that targets Bcr-Abl, *KIT* and *PDGFR*, which is orally administered. Consequently the prognosis of patients with advanced GIST has been spectacularly improved. Up to 85% of GIST patients with advanced disease derive clinical benefit from imatinib 400mg daily.(7) For patients with high-risk of recurrence (10 year recurrence rate >50%), adjuvant treatment with imatinib for a total of 3 years is recommended.(8,13) This increased progression-free survival (PFS) from 36% to 65.6%. Compared to 1 year of adjuvant imatinib treatment overall 5-year survival was also reported to improve with 3 years adjuvant imatinib treatment (92.0% vs 81.7%).(13)

Neo-adjuvant treatment with imatinib is recommended in patients with locally advanced disease when resection with positive margins or clear perioperative morbidity is expected.(8) Imatinib is used to downsize the tumor. Surgery is performed when maximum radiological response is achieved. In general, this is the case after 6 to 12 months of imatinib treatment.(14)

The effect of TKIs depends on the type of mutation. It is therefore important to assess *KIT* and *PDGFR* mutation status before the initiation of adjuvant or neoadjuvant therapy. (15,16) For instance, imatinib 400mg shows less benefit in GISTs harboring a mutation in *KIT* exon 9 and studies in advanced GISTs shows that the use of a 800mg imatinib in this case is more beneficial.(17) A D842V substitution in exon 18 of the *PDGFRA* gene, shows primary resistance to imatinib.(18) Furthermore, GISTs who are wild type for *KIT* and *PDGFRA* are less sensitive and even show primary resistance to imatinib treatment.

In metastatic disease, imatinib treatment with a standard dose of 400mg daily is used as first-line systemic palliative treatment. Therapy is continued until disease progression. Median progression-free survival in advanced disease is 20-24 months and overall survival is 5 years. Interestingly, around 20% of patients live longer than 10 years. (19) When the disease progresses this is often (80%) caused by a secondary mutation in the *KIT* gene. (20) In general these mutation occur in the ATP binding pocket of the *KIT* gene (exons 13 and 14).(21) Secondary mutations occur heterogeneously across different lesions, but can also vary within one lesion. Debate is still ongoing whether resection of the (single) progressive metastasis in case of limited progression is beneficial.(22) Some studies also advocate a dose escalation of imatinib to 800 mg daily.(17,23) This could be effective in case of secondary resistant mutations, but can also increase efficacy in patients with a low drug exposure as pharmacokinetic variability is high.(24)

Side effects of imatinib treatment are mostly mild and clinically manageable.(25,26) In general permanent discontinuation of treatment because of toxicity can be avoided. Most common side effects are edema (mostly periorbital), nausea, diarrhea, myalgia, fatigue, skin toxicity, headache and pain. Also, hematologic side effects are common with up to 90% of GIST patients having anemia and up to 40% having neutropenia.(25,26)

In case of progression or intolerance to imatinib, sunitinib has become a registered second line treatment. Sunitinib is a TKI that targets vascular endothelial growth factor

receptor (VEGFR), PDGFR, KIT and, and colony stimulating factor receptor (CSF-1R). It has been proven effective in a dose regimen of 50 mg daily '4-weeks on-2 weeks off'.(27) Median PFS was 27 weeks compared to 6 weeks in the placebo arm. Continuous dosing in a dose of 37.5 mg is reported to be equally effective with similar tolerance.(28) Regorafenib, a TKI targeting VEGFR, KIT, PDGFR, fibroblast growth factor receptor (FGFR), and RET has been registered in Europe in 2014 as an acknowledged third line treatment in progressive disease. In a dosing schedule of 160 mg daily every three of four weeks regorafenib has demonstrated to improve progression-free survival for up to 4 months.(29)

Response evaluations and follow-up

Computed tomography (CT) scans are considered standard in the response evaluation in routine clinical care.(8,30,31) On CT scan the anti-tumor activity does not only translate into decrease in size, but also in decrease in density. Prior research has shown that response evaluation using both tumor size and density (CHOI criteria) is better correlated with time to progression compared to standard Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The use of RECIST criteria might lead to underestimation of the effectiveness of TKI's in GIST.(32,33)

MRI usually provides better preoperative staging information in case of rectal GISTs. ^{18}F-flurodeoxyglucose (FDG)-positron emission tomography (PET) has proven to be an effective way for early response evaluation of systemic treatment.(34) There is still a lot of debate on the role of PET in routine clinical care.

More important, there is no known optimal follow-up schedule for patients with GIST. ASCO and ESMO guidelines for the diagnosis and treatment of GIST patients do exist. However, routine follow-up schedules still differ across treatment centers and countries. (8,30)

The Dutch GIST Registry

In January 2014 the Dutch GIST Consortium (DGC) was established by the five leading GIST centers in the Netherlands, the Netherlands Cancer Institute/Antoni van Leeuwenhoek (NKI/AvL), Leiden University Medical Center (LUMC), Erasmus Medical Center (EMC), Radboud University Medical Center Nijmegen (Radboud UMC) and University Medical Center Groningen (UMCG). In January 2014 the DGC has initiated the Dutch GIST Registry The GIST registry includes a retrospective dataset as well as a prospective dataset. Retrospective data has been collected from all patients treated in five GIST centers in the Netherlands between 2009 and 2014. Prospectively, data is collected from patients diagnosed with GIST and treated in one of the GIST centers from January 2014 and onwards.

Approximately 200 variables per patient are entered in the registry. The variables include patients' demographics, tumor characteristics including pathological and genetic information, systemic therapies with their start and stop dates, adverse events with start

and stop dates, any GIST related surgery, medical history and co-medication. In addition, the data obtained during hospital visit are put in the database, containing physical examination, laboratory results, tumor measurements by any imaging technique (e.g. CT-scan, MRI, PET-CT), electrocardiography results and QOL results.

Outline of the thesis

The focus for this thesis will be on treatment strategies and follow-up in GIST patients and in particular subgroups of GIST patients in daily clinical practice. In the first part of this thesis (Chapter 2) clinical characteristics and treatment patterns of different subgroups of GIST patients will be assessed.

An important subgroup are the elderly GIST patients (> 75 years of age). Paragraph 2.1 will assess differences in local treatment and systemic treatment between elderly patients and younger patients treated in one of our 5 GIST centers.

A second important subgroup are the patients with a *PGFDRA* mutated GIST. *PDGFRA* mutated GISTS are very rare. A D842V substitution in exon 18 is the most common *PDGFRA* mutation. The specific mutation in exon 18 of *PDGFRA* is essential for their sensitivity to imatinib treatment. Paragraph 2.2 describes treatment response in a cohort of GIST patients harboring various *PDGFRA* exon 18 mutations.

A third important subgroup of GIST patients are the patients with underlying germline mutations. Although GISTs harboring a *KIT* mutation are almost always sporadic, familial GISTs associated with germline *KIT* or *PDGFRA* mutations do occur. Paragraph 2.3 reports the effects of imatinib on the tumor and on the cutaneous hyperpigmentation associated with this rare syndrome.

Despite the spectacular improvements in the treatment of GIST since the introduction of imatinib, disabling and even life-threatening adverse events can occur. In chapter 3 the occurrence and management of agranulocytosis is described.

Follow-up and assessment of treatment effects are described in chapter 4 and 5. In chapter 4 the value of ^{18}F-flurodeoxyglucose (FDG)-positron emission tomography (PET) in the management of GIST patients treated in neo-adjuvant (4.1) and palliative setting (4.2) is assessed. Chapter 5 describes the pharmacokinetics and occurrence of underexposure of imatinib in a large observational cohort of GIST patients with over 400 drug levels measured in more than 100 patients during routine outpatient care. Finally, in chapter 6 the content of this thesis and future prospects in the treatment of GIST are discussed.

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2

Chapter 2

Special GIST populations

Paragraph 2.1

Elderly patients with gastrointestinal stromal tumor (GIST) receive less treatment irrespective of performance score or comorbidity - A retrospective multicenter study in a large cohort of GIST patients

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Abstract

Objective

Although gastrointestinal stromal tumors (GIST) predominantly occur in older patients, data on treatment patterns in elderly GIST patients are scarce.

Methods

Patients registered in the Dutch GIST Registry (DGR) from January 2009 until December 2016 were included. Differences in treatment patterns between elderly (75 years) and younger patients were compared. Multivariate analyses were conducted using logistic regression.

Results

Data of 145 elderly and 665 non-elderly patients were registered (median age 78 and 60 years respectively). In elderly patients, performance score (WHO-PS) and age-adjusted Charlson Comorbidity Index (ACCI) were significantly higher ($p < 0.05$; $p < 0.001$), and albumin level significantly lower ($p = 0.04$). Hundred-and-nine (75.2%) elderly and 503 (75.6%) non-elderly patients had only localized disease. Surgery was performed in 57% of elderly versus 84% of non-elderly patients ($p = 0.003$, OR: 0.26, 95% CI: 0.11-0.63). No differences in surgery outcome or complications were found. Thirty-eight percent of elderly with an indication for adjuvant treatment did receive imatinib versus 68% of non-elderly ($p = 0.04$, OR: 0.47, 95% CI: 0.23-0.95). Thirty-six elderly and 162 non-elderly patients had metastatic disease. Palliative imatinib was equally given (mean dose 400 mg) and adverse events were mostly minor ($p = 0.71$). In elderly, drug-related toxicity was in 32.7% reason to discontinue imatinib versus 5.1% in non-elderly ($p = 0.001$, OR 13.5, 95% CI: 2.8-65.0). Median progression-free survival (PFS) was 24 months in elderly and 33 months in non-elderly ($p = 0.10$). Median overall survival (OS) was 34 months and 59 months respectively ($p = 0.01$).

Conclusions

Elderly GIST patients with localized disease receive less surgery and adjuvant treatment, irrespective of comorbidity and performance score. Drug-related toxicity results more often in treatment discontinuation. This possibly results in poor outcome.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal tract. Annual incidence is estimated to be between 11 and 19.6 per million worldwide.(1) The highest incidence is found in the age group of 60-74 years, closely followed by patients 75 years of age and older.(2) The latter age group is growing as life expectancy continues to increase. Besides, patients 75 years of age and older have an estimated life expectancy of up to 12 years.(3) Nevertheless, studies on treatment strategies in elderly GIST patients are scarce.

Since the introduction of imatinib, a tyrosine kinase inhibitor (TKI) that targets Bcr-Abl fusion gene, *KIT* and platelet-derived growth factor receptor (*PDGFR*), treatment of patients with advanced GIST has been spectacularly improved. Up to 85% of GIST patients with advanced disease derive clinical benefit from imatinib.(4) One retrospective study in GIST patients 75 years of age and older with advanced disease found survival rates similar to survival rates described in the overall GIST population.(5)

In patients with resectable localized disease, primary therapy consists of surgery. For patients with high-risk of recurrence, adjuvant treatment with imatinib is recommended. (6,7)

Despite this recommendation, a prior study showed that adjuvant treatment with imatinib in patients with high-risk disease is significantly less frequently given in patients 65 years of age and older.(8) As frailty, disability, and multimorbidity are more common in the elderly population, treatment decisions might be influenced.(9) The aim of this study was to assess differences in treatment strategies between elderly patients (aged 75 years) and younger patients (<75 year old) with GIST.

Methods

Patients

All patients entered in the Dutch GIST Registry (DGR) were included in this cohort analysis. This database includes all GIST patients treated between January 2009 and September 2016 in one of five GIST expert centers in the Netherlands: the Netherlands Cancer Institute/ Antoni van Leeuwenhoek Hospital, Leiden University Medical Center, Erasmus University Medical Center, Radboud University Nijmegen Medical Center and the University Medical Center Groningen. Data acquisition was approved by local independent ethics committees, and the study was conducted in accordance with the Declaration of Helsinki.

Variables

Baseline demographic data, such as sex, age, ethnic origin, baseline World Health Organization Performance Score (WHO PS) and baseline albumin level and comorbidities, were retrieved from the DGR. Comorbidities were scored using the Charlson Comorbidity

Index (CCI).(10) Tumor-specific data, such as location, size, mitotic rate and mutation status were also retrieved from this database. Tumor measurements were derived from computed tomography (CT) scans, positron emission tomography (PET) scans, and magnetic resonance imaging (MRI).

For systemic treatment, the database includes treatment objective, treatment type (imatinib, sunitinib, regorafenib or other), dose, duration of treatment and reasons for treatment interruptions. Also, adverse events during systemic treatment were entered and assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. For surgery, reasons for surgery, surgery technique (endoscopy, laparoscopic and open laparotomy), extent of surgery and surgery outcome have been registered.

Statistical analyses

Statistical analyses were executed using IBM SPSS Statistics 23. Cut-off date for clinical outcome was 28th December 2016. For this analysis, patients with a lower age limit of 75 years or older were defined as elderly, in accordance to prior studies in both GIST and general geriatric oncology.(5,11,12) Analyses on adjuvant treatment strategies were assessed only in patients who had a high-risk (>50% risk of recurrence according to Miettinen's criteria) GIST resected and who had a registration date starting from March 2011.(13) From this date adjuvant imatinib treatment was officially implemented in the Netherlands.(14) Differences be-tween elderly patients and younger patients were assessed using the Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. Variables with a p-value < 0.05 in univariate analyses were included in the multivariate analyses using a logistic regression model. Progression-free survival (PFS) was calculated in patients receiving systemic treatment with palliative intent and was defined as the time from start of treatment until disease progression, death or last patient contact. Overall survival (OS) was calculated in patients with localized disease and patients with metastatic disease separately and was defined as the time of registration in the hospital until death or last contact. Survival analysis was conducted using the Kaplan-Meier method. All tests were two-sided and a p-value of <0.05 was considered significant.

Results

Demographic characteristics

In total 810 patients were entered in the DGR of whom 145 (17.6%) patients were 75 years of age and older. Table 1 shows differences in demographic characteristics between elderly and non-elderly patients. Baseline WHO PS and age-adjusted CCI score were significantly higher in elderly patients, albumin level was significantly lower (Table 1).

Patients with localized disease

In total, 109 elderly and 503 non-elderly patients in the DGR had non-metastatic disease. Surgery was per-formed in 57% of the elderly compared to 84% in the non-elderly ($p < 0.001$) (Table 2). No significant differences in surgery technique, type, surgical outcome or complications were found (Table 3). In multivariate analyses, elderly were still less likely to receive surgery ($p = 0.003$, OR 0.26, 95% CI: 0.11-0.63). Furthermore, 8 out of 20 (38%) of elderly patients with an indication for adjuvant treatment did receive imatinib in adjuvant setting compared to 78 out of 112 (68%) of the non-elderly ($p = 0.03$) (Table 2). Also in multivariate analyses adjuvant treatment was initiated less in elderly ($p = 0.04$, OR 0.47, 95% CI: 0.23-0.95). In addition, in univariate analyses elderly patients with localized disease were more likely to receive imatinib with palliative intent ($p = 0.05$), but multivariate analysis showed no significant difference ($p = 0.07$, OR 1.70, 95% CI: 0.73-3.96). Fifteen elderly with localized disease (10.3%) received no treatment at all, compared to 20 non-elderly (3.0%; $p< 0.01$). Follow-up was terminated in 44 elderly (41.1%) and in 89 non-elderly (17.8%). Median follow-up time in elderly was 30 months (95% CI: 23.23-36.32) and was 74 months (no 95% CI could be calculated) in non-elderly ($p < 0.001$) (Figure 1). Sixteen elderly with localized disease (15.0%) died during follow-up, of whom 6 of disease progression (5.6%). In the non-elderly group 39 patients (7.8%) died, 12 of disease progression (2.4%). Median OS was not reached.

Patients with metastatic disease

In total, 36 elderly had metastatic disease at registry entry. Imatinib was given in 86% of elderly patients (Table 4). The mean daily dose of imatinib was 400 mg for elderly compared to 395 mg for non-elderly ($p = 0.33$). Also, second- and third-line therapy were given equally in elderly and non-elderly (Table 4). Adverse events were equally common in elderly and non-elderly (71.4% and 69.4% respectively). Most adverse events in both groups were grade 1 or 2 (54.5% and 58.7% respectively) and no differences were found in occurrence of grade 3 adverse events ($p = 0.71$) (Table 5). In 28 (57.1%) elderly with metastatic disease imatinib treatment was discontinued compared to 75 (38.3%) non-elderly ($p = 0.017$). The most common reason to end imatinib treatment in elderly patients was an adverse event (57.1%). In non-elderly this was 13.3% ($p < 0.001$). In elderly, progressive disease was in 38.1% of cases reason to end systemic treatment compared to 77.6% of non-elderly. In multivariate analysis, corrected for WHO PS, CCI, and albumin level, this difference was still significant ($p = 0.001$, OR 13.5, 95% CI: 2.8-65.0).

Table 1: Patient characteristics.

Characteristics	Elderly (75 year old) N = 145	Non-elderly (<75 year old) N = 665	p-value[a]
Age (median; range)	7 (75-92)	60 (15-74)	<0.001
Sex			0.56
Male	74 (51.0%)	357 (53.7%)	
Female	71 (49.0%)	308 (46.3%)	
Primary tumor location			0.19
Gastric	93 (64.1%)	371 (55.8%)	
Small bowel	28 (19.3%)	159 (23.9%)	
Duodenal	5 (3.4%)	51(7.7%)	
Oesophagus	2 (1.4%)	6 (0.9%)	
Rectum	12 (8.3%)	41(6.2%)	
Colon	0 (0.0%)	8 (1.2%)	
Other	5 (3.4%)	29(4.4%)	
Tumor size in mm at baseline (Median; range)	81 (4-290)	90 (2-340)	0.79
Tumor status at registry entry			0.95
Localized disease	75 (50.8%)	338 (51.7%)	
Locally advanced[b]	30 (22.6%)	150 (20.7%)	
Metastatic disease	36 (24.4%)	162 (24.8%)	
Other/not reported	4 (2.8%)	15 (2.3%)	
Tumor histology			0.51
Spindle cell	89 (61.4%)	419 (63.0%)	
Epithelioid	14 (9.7%)	51 (7.7%)	
Mixed type	12 (8.3%)	72 (10.8%)	
Not reported	30 (20.6%)	123 (19.4%)	
Number of mitoses per 5 mm^2			0.59
≤5 mitoses	68 (46.9%)	335 (50.4%)	
>5 mitoses	36 (24.8%)	200 (30.1%)	
Not reported	41 (28.2%)	130 (19.6%)	
Risk category			0.38
Low risk	88 (60.7%)	376 (56.6%)	
High risk	34 (23.4%)	194 (29.2%)	
Unknown	23 (15.9%)	95 (14.3%)	
Mutation status			0.72
KIT mutation			
Exon 11	66 (45.5%)	317 (47.7%)	
Exon 9	6 (4.1%)	37(5.6%)	
Exon 13	2 (1.4%)	7 (1.1%)	

Exon 17	0 (0.0%)	3 (0.5%)	
Not further specified	2 (1.4%)	6 (0.9%)	
PDGFRA mutation			
Exon 18	12 (8.3%)	52 (7.8%)	
Exon 14	0 (0.0%)	4 (0.6%)	
Exon 12	2 (1.4%)	5 (0.8%)	
Not further specified	1 (0.7%)	2 (0.3%)	
WT for *KIT* and *PDGFRA*	7 (4.8%)	58 (8.7%)	
Unknown mutation	47 (32.4%)	174 (26.2%)	
Baseline WHO performance status			0.045
WHO 1	62 (42.8%)	290 (43.6%)	
WHO 2	13 (9.0%)	27 (4.1%)	
Not reported	70 (48.3%)	348 (52.3%)	
Age-adjusted Charlson comorbidity index score			<0.001
≤5	109 (75.2%)	633 (95.2%)	
>5	36 (24.8%)	32 (4.8%)	
Charlson comorbidity index score without age			0.20
≤5	139 (95.9%)	650 (97.7%)	
>5	6 (4.1%)	15 (2.3%)	
Baseline albumin level			0.04
Median (range)	41 (25-50)	43 (20-62)	

[a] Univariate analyses using Chi-square test for categorical variables and Mann-Whitney U for continuous variables.

[b] Defined as GISTs needing neo-adjuvant imatinib treatment before surgery is deemed possible or safe.

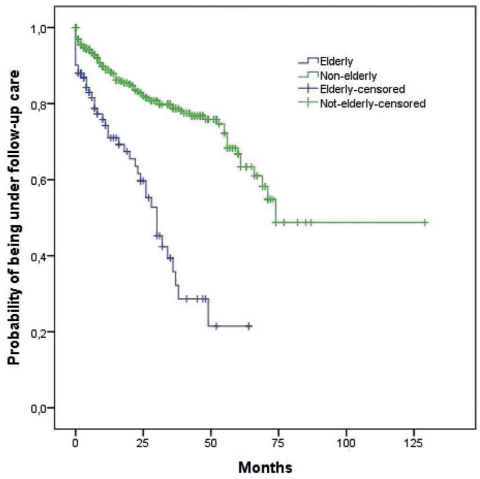

Figure 1: Difference in duration of follow-up care between elderly and non-elderly patients with localized disease.

No difference in PFS was found (p = 0.70). Median PFS was 24 month (95% CI: 13.3-34.7) in elderly compared to 33 months in non-elderly (p = 0.10, 95% CI: 27.4-38.6) (Figure 2). Multivariate Cox regression including WHO PS, baseline albumin level, and CCI still did not show any significant differences in PFS (p = 0.81). Twelve elderly (33.3%) and 31 non-elderly (19.1%) patients with metastatic disease have died during follow-up. Nine elderly (25.0%) and 26 non-elderly (16.0%) have died of disease progression. Median OS was 34 months in elderly patients (95% CI: 13.0-55.0) and 59 months in non-elderly (no 95% CI could be calculated) and was significantly shorter in elderly patients (p = 0.01) (Figure 3).

Table 2: Treatments given in patients with localized disease.

Treatment[a]	Elderly N = 107	Non-elderly N = 500	p-value[b]
Systemic treatment with imatinib	53 (49.5%)	270 (54.0%)	0.40
Neo-adjuvant	32 (29.9%)	163 (32.6%)	0.59
Adjuvant[c]	6 (37.5%)	52 (65.8%)	0.03
Palliative	18 (16.8%)	51 (10.2%)	0.05
Surgery	61 (57.0%)	420 (84.0%)	<0.001

[a] Note that the numbers do not add up since multiple treatments can be given consecutively in one individual patient.
[b] Univariate analyses using Chi-square test.
[c] Adjuvant treatment is only calculated in high-risk GIST patients with a registration date after March 2011 who had surgery (N = 16 in elderly patients and N = 79 in non-elderly patients).

Table 3: Surgery type and outcome in patients with localized disease.

Surgery characteristics	Elderly N = 61	Non-elderly N = 420	p-value[a]
Reason for surgery			0.37
Planned operation for GIST	46 (75.4%)	316 (75.4%)	
Planned for other tumor	6 (9.8%)	63 (15.0%)	
Emergency	8 (13.1%)	28 (6.7%)	
Other/unknown	0 (0.0%)	13 (3.0%)	
Surgery technique			0.82
Open laparotomy	54 (88.5%)	355 (84.5%)	
Laparoscopy	5 (8.2%)	45 (10.7%)	
Endoscopy	1 (1.6%)	7 (1.7%)	
Unknown	1 (1.6%)	13 (3.1%)	
Surgery type			0.09
Limited or local surgery	49 (80.3%)	347 (82.6%)	
Typical organ resection	8 (13.1%)	23 (5.5%)	
Multivisceral resection	4 (6.6%)	37 (8.8%)	
Other/unknown	0 (0.0%)	13 (3.1%)	
Tumor size resected			0.68
<100 mm	41 (67.2%)	268 (63.8%)	
100 mm	15 (24.6%)	112 (26.7%)	
Unknown	5 (8.2%)	40 (9.5%)	
Tumor rupture			0.64
No	45 (73.8%)	309 (73.6%)	
Yes, preoperative[b]	5 (8.2%)	21 (5.0%)	
Yes, intraoperative	3 (4.9%)	20 (4.8%)	
Unknown	8 (13.1%)	70 (16.7%)	
Surgery result			0.47
R0	56 (91.8%)	365 (86.9%)	
R1	4 (6.6%)	26 (6.2%)	
R2	0 (0.0%)	10 (2.4%)	
Unknown	1 (1.65)	19 (4.5%)	
Perioperative complications			0.16
No	42 (68.9%)	309 (73.6%)	
Yes, but not leading to reoperation	9 (14.8%)	36 (8.6%)	
Yes, leading to reoperation	6(9.8%)	18 (4.3%)	
Other/unknown	4 (6.6%)	57 (13.6%)	

[a] Univariate analyses using Chi-square test.

[b] Preoperative tumor rupture is defined as tumor rupture causing visible (perioperative or on preoperative imaging scans) spill or described by the pathologist as an entire interruption of the tumor wall and was preexisting before surgery (as described in the surgical report).

Table 4: Treatments in patient with metastatic disease.

Treatment[a]	Elderly N = 36	Non-elderly N = 162	p-value[b]
Systemic treatment	31 (86.1%)	150 (92.6%)	0.21
Imatinib	31 (86.1%)	147 (90.7%)	0.40
Sunitinib	10 (27.8%)	54 (33.3%)	0.52
Regorafenib	1 (2.8%)	17 (10.5%)	0.15
Metastasectomy	3 (5.9%)	23 (8.3%)	0.55

[a] Note that the numbers do not add up since multiple treatments can be given consecutively in one individual patient.
[b] Univariate analyses using Chi-square test.

Table 5: Occurrence of adverse events grade 3 related to imatinib treatment.

Treatment[a]	Elderly N = 36	Non-elderly N = 162
Nausea	1 (1.2%)	8 (1.9%)
Fatigue	2 (2.4%)	5 (1.2%)
Diarrhoea	-	5 (1.2%)
Skin toxicity	5 (5.9%)	7 (1.7%)
Arthralgia	-	1 (0.2%)
Infection	3 (3.5%)	10 (2.4%)
Neutropenia	1 (1.2%)	5 (1.2%)
Gastrointestinal haemorrhage	-	8 (1.9%)
Periorbital oedema	1 (1.2%)	1 (0.2%)
Pain	-	7 (1.7%)
Generalised oedema	-	1 (0.2%)
Anaemia	9 (10.6%)	16 (3.9%)
Ascites	1 (1.2%)	6 (1.4%)
Myalgia	-	1 (0.2%)
Increase in creatinine	-	9 (2.2%)
Dyspnoea	2 (2.4%)	3 (0.5%)
Thrombocytopenia	-	1 (0.2%)
Other	6 (7.1%)	24 (5.8%)
Total[a]	22 (25.9%)	84 (20.2%)

[a] Note that the total number of patients does not add up since multiple adverse events can occur in one patient.

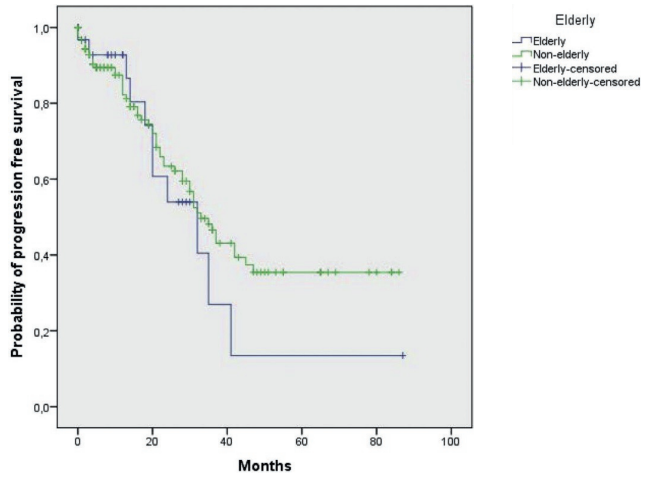

Figure 2: Difference in progression-free survival between elderly patients and non-elderly patients with metastatic disease.

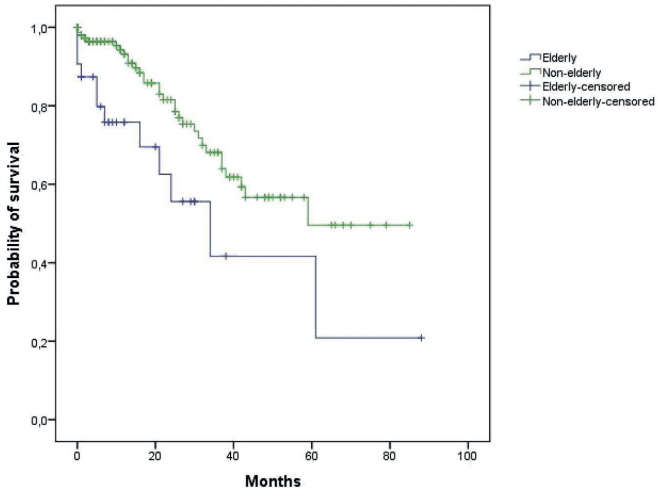

Figure 3: Difference in overall survival between elderly and non- elderly patients with metastatic disease.

Discussion

GISTs have a high incidence in the age group of 75 years of age and older.(2) However, studies on treatment strategies in elderly GIST patients are scarce as, in general, elderly cancer patients are underrepresented in trials.(12) This is a problem since life expectancy is increasing. Currently in the Netherlands, elderly patients 75 years have an average life expectancy of up to 12 more years.(3) As frailty, disability and comorbidity are more common in the elderly population, treatment decisions may very well be influenced by these factors.(9) In our study, we indeed found that elderly patients had worse WHO PS and lower albumin level. However, irrespective of performance status or comorbidity, elderly GIST patients with localized disease received less treatment. Surgery was significantly less performed in the elderly. Meanwhile, in elderly patients who did receive surgery no difference in occurrence of major complications was found. One might argue that this is caused by successful selection of patients eligible for surgery. Especially since in our study almost 90% of surgery was conducted by open laparotomy. Meanwhile, recent studies suggest that less invasive surgery, like laparoscopic and even endoscopic resection, is feasible and safe for poor PS elderly patients.(15,16) This might be an option for elderly patients who are deemed not eligible for open surgery.

In addition, adjuvant treatment was given significantly less in elderly patients after resection of a high-risk tumor. Our findings are similar to a prior study, where adjuvant treatment with imatinib in high-risk patients was significantly less given in patients 65 years of age and older.(8) However, it is well known that recurrence in high-risk patients often occurs and studies showed that adjuvant treatment with imatinib for 36 months increased 5-year recurrence-free survival (RFS) from 36% to 65.6%.(17,18) Considering the increasing life expectancy in elderly patients, adjuvant imatinib treatment might be beneficial, even in this age group. Besides, occurrence of adverse events related to imatinib treatment and dose of imatinib in our study was the same in the elderly and non-elderly group, suggesting equal tolerance to imatinib. Considering the low number of events, no RFS could be calculated in our cohort. However, slightly more elderly with localized disease have died of disease progression. An earlier study on age-related risk factors in GIST patients has also found worse disease-specific survival rates in elderly patients compared to patients younger than 50 years of age.(19) Similar to our study, they did not find any differences in tumor characteristics, suggesting that worse disease-specific survival rates can be explained by lack of treatment in elderly patients. Moreover, in our registry less than 18% of the GIST patients are 75 years of age and older at diagnosis, while in the Netherlands this is estimated to be approximately 25% annually.(2) This suggests that a relatively large proportion of elderly GIST patients are not referred to a GIST center, possibly resulting in a greater number of elderly GIST patients who do not receive treatment. It is unclear why less treatment is given in our elderly population with localized disease. One explanation might be that besides the physician's expert opinion, the elderly patient him-self might be less motivated for treatment.

In contrast to elderly with localized disease, elderly patients with metastatic disease are treated in a similar manner to non-elderly patients. Consistent with a prior study in elderly GIST patients aged 75 years with advanced disease, we found that first-, second- and third-line treatment are equally initiated in the elderly and non-elderly group.(5) Also, no difference in treatment efficacy or occurrence of adverse events was found. Similar to the study of Italiano et al., adverse events were mainly of grades 1 and 2. In their study they mention that most adverse events were medically manageable and dose reduction occurred in almost 50% of the cases.(5) In our study, however, mean imatinib dose was 400 mg in the elderly, suggesting that dose reductions rarely occurred in our population. It seems that adverse events were more often managed by treatment interruption rather than reducing imatinib dose. This might have caused a significantly shorter overall survival in elderly. Meanwhile, in the abovementioned study a dose reduction seemed not to result in worse survival rates. On the other hand, there is evidence that imatinib underexposure is associated with worse treatment outcome.(20,21) This might explain why in our study in case of an adverse events dose reduction rarely occurred. Also, rather than a decision made by the clinician, this might also be a patient-motivated decision. An earlier study on compliance to treatment in GIST patients found that older GIST patients showed more non-compliance to therapy.(22) A dose reduction might improve compliance to therapy in elderly patients. Moreover, considering the large interpatient variability, imatinib plasma levels give more insight in drug efficacy in the individual patient than dose does. Therapeutic drug monitoring (TDM) might therefore be useful in elderly patients with adverse events and might result in dose reduction without reducing treatment efficacy. Considering earlier findings, in our opinion a dose reduction seems to be a better advice than discontinuation of treatment.(5,23)

In conclusion, primary resection and adjuvant imatinib treatment seem feasible and effective treatments in elderly GIST patients with localized disease. However, irrespective of PS or comorbidity these patients receive less treatment. An objective evaluation of comorbidity using the CCI might improve the decisions-making process in elderly GIST patients. In case of adverse events during imatinib treatment a dose reduction is preferred rather than treatment discontinuation.

Conflicts of interest statement

Neeltje Steeghs received a research grant for the Dutch GIST Registry from Novartis, Pfizer and Bayer.

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Paragraph 2.2

Clinical characteristics and treatment outcome in a large multicenter observational cohort of *PDGFRA* exon 18 mutated gastrointestinal stromal tumor patients

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Abstract

Purpose

Platelet-derived growth factor receptor alpha (*PDGFRA*) D842V-mutated gastrointestinal stromal tumors (GISTs) are known for their insensitivity to imatinib. However, in clinical practice responses have been observed in some patients. We describe the natural history and treatment outcomes in a cohort of *PDGFRA* exon 18 mutated GIST patients.

Patients and methods

A retrospective cohort study was conducted in *PDGFRA* exon 18 mutation GIST patients treated in six expert centers in the Netherlands and the United States. Two independent radiologists assessed radiological response to imatinib according to Choi's criteria in all patients with measurable disease treated with imatinib in neo-adjuvant or palliative intent.

Results

Seventy-one patients with *PDGFRA* exon 18 mutation were identified of whom 48 patients (69%) had a D842V mutation. Twenty-two (45.8%) D842V-mutated GIST patients received imatinib treatment, 16 had measurable disease. Fourteen out of the 23 (60.9%) patients with non-D842V mutations received imatinib treatment, eight had measurable disease. Two out of 16 (12.5%) D842V-mutated GIST patients had partial response, 3 patients (18.8%) had stable disease, and 9 patients (56.3%) had progressive disease as best response. Two patients did not have follow-up computed tomography scans to assess response. Six out of 8 (75%) patients with non-D842V exon 18 mutations had partial response and two (25%) had stable disease as best response.

Conclusion

Patients with D842V-mutated GISTs can occasionally respond to imatinib. In the absence of better therapeutic options, imatinib should therefore not be universally withheld in patients with this mutation.

Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. Important to their tumorigenesis is an activating mutation involving a gene, which encodes for a tyrosine kinase receptor (TKR). Most commonly, this TKR is *KIT* (w75%) and in 10% of patients, platelet-derived growth factor receptor alpha (*PDGFRA*). Approximately 15% of all GISTs are wild type for *PDGFRA* and *KIT*.(1)

Systemic treatment with imatinib, an oral tyrosine kinase inhibitor (TKI), has been proven effective for a majority of patients with advanced GIST, showing response in up to 85% of advanced GIST patients.(2) In addition, patients with an operable GIST with a high risk of recurrence can improve their progression-free survival (PFS) with adjuvant imatinib. For these patients, adjuvant treatment with imatinib for 36 months increased PFS from 36% to 65.6%.(3,4) However, the affinity of TKIs depends on the type of mutation. The most common *PDGFRA* mutation, a D842V substitution in exon 18, shows primary resistance to imatinib in in vitro and in vivo studies.(5-7) Although D842V-mutated GISTs comprise a large majority of *PDGFRA* exon 18 GISTs, other mutations in exon 18 differ in their sensitivity to imatinib. It is therefore important to distinguish between resistant and sensitive mutations. However, few non-D842V GISTs have been described.(5,6,8)

According to the international guidelines, adjuvant treatment is not recommended for patients with D842V-mutated GIST.(9) However, there are no specific recommendations on treatment of these GIST patients with advanced disease.(9,10) Despite expected resistance to imatinib, some advanced D842V-mutated GIST patients end up receiving imatinib either because of an unknown mutation status at the time of treatment or due to the absence of better therapeutic options. In our daily practice we noted some D842V-mutated GIST patients who appeared to respond to imatinib treatment. Based on these anecdotal findings we conducted an observational study including data from six expert centers in the Netherlands and the United States. We describe treatment and responses in all GISTs harboring a mutation in *PDGFRA* exon 18.

Methods

Patient population

Three cohorts of patients were defined: (1) patients included in the Dutch GIST Registry (DGR); (2) patients with a *PDGFRA* exon 18 mutation identified from the pathology database of the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI-AvL) in Amsterdam, Netherlands and (3) patients with a *PDGFRA* exon 18 mutation identified from the pathology database of the MD Anderson Cancer Center (MDACC), Houston, USA.

The DGR includes all GIST patients diagnosed with GIST between January 2009 and March 2015 in the 5 GIST centers in the Netherlands: the NKI-AvL, Leiden University

Medical Center, Erasmus University Medical Center, Radboud University Nijmegen Medical Centerand the University Medical Center Groningen.

Within the pathology database of the NKI-AvL all GIST patients diagnosed before January 2009 with *PDGFRA* exon 18 mutations were identified. Patients identified from the pathology databases were included in the analyses when a medical record was available. Data acquisition was approved by the local independent ethics committees, and the study was conducted in accordance with the Declaration of Helsinki.

Clinical data selection

The DGR contains demographic and clinical variables, including age, sex, relevant family history and primary tumor location, size and stage. Furthermore, pathology reports describing histology, immunohistochemistry and mutational status are entered in the database. Local and systemic therapies and all hospital visits were registered, including computed tomography (CT) scans and mag-netic resonance imaging. For patients who were not entered in the DGR, clinical data points were collected using medical records.

Molecular diagnosis

For MDACC patients, polymerase chain reaction (PCR) based DNA sequencing for *KIT* and *PDGFRA* was performed at the Molecular Diagnostics Laboratory at the University of Texas MDACC. Formalin fixed paraffin-embedded blocks with tumor were selected and 4 mm-thick sections prepared. Genomic DNA samples were isolated from micro-dissected paraffin-embedded slides using a QIAamp DNA miniKIT (Qia-gen, Germantown, MD, USA). For PCR, primer sets for exons 9, 11, 13 and 17 of the *KIT* gene and for exon 18 of the *PDGFRA* gene were used. PCR was carried out in a total volume of 25 ml containing 50e100 ng of genomic DNA and 0.25 ml of DNA polymerase (Bioline, London, UK). Mutations were identified by sequencing the PCR products on a 3730 1 DNA analyzer (Applied Biosystems, Carlsbad, CA, USA).

For most Dutch sites, routine mutation analysis included analysis of *KIT* (exons 9, 11, 13 and 17) and *PDGFRA* (exons 12, 14 and 18) by Sanger Sequencing. Five to 10 mm formalin fixed paraffin embedded (FFPE) sections of tumor material were used for DNA isolation using standard procedures (KAPA Express Extract KIT, Kapa Biosystems, Massachusetts, USA). An area for micro-dissection of tumor cells was indicated by a pathologist. Sequencing was performed on a capillary sequencer (ABI 3730 DNA Analyzer, Life Technologies, USA), mutation analysis was performed using specific software (Mutation Surveyor, Softgenetics, USA).

For validation purposes, repeated molecular analyses were performed in samples from multiple sites of the resected tumors for all patients with a D842V-mutated GIST with partial response (PR).

Radiological response evaluation

In all patients with measurable disease treated in neo-adjuvant or palliative setting radiological tumor measurements were re-evaluated by two independent radiologists using Choi's criteria: PR was defined as at least 10% decrease in maximal diameter as measured ac-cording to Response Evaluation Criteria in Solid Tumors (RECIST) or 15% decrease or more in Hounsfield units; progressive disease (PD) was determined in case of an increase in tumor diameter of 10% and if the tumor does not meet the PR criteria by tumor attenuation on CT; if the tumor did not meet either of the criteria for PR or PD, response was defined as stable disease (SD).(11) If the outcomes of both radiologists did not correspond, an outcome was determined based on consensus.

Pathological response evaluation

Histologic response evaluation was conducted in patients who received imatinib prior to surgery. Response was graded based on the microscopic amount of necrosis and fibrosis according to the following scheme that is based on consensus between pathologists in the MD Anderson and the NKI-AvL: (1) minimal, <10%; (2) moderate, 10-50% and (3) good, >50%. Grading was done at the MDACC and in the AvL-NKI population separately.

Statistical analysis

Median time to progression (TTP) was calculated for all patients with measurable disease treated with neo-adjuvant or palliative intent. It was calculated from the date of initiation of imatinib treatment to the date of radiological or clinical progression prompting the physician to change treatment strategy. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 22.0.

Results

Patient numbers

In the DGR, 678 GIST patients were identified of whom 42 patients with GIST harboring a mutation in *PDGFRA* exon 18. The pathology databases of the NKI-AvL and the MDACC revealed 29 additional *PDGFRA* exon 18 mutated GIST patients; 10 at the NKI-AvL and 19 at the MDACC. In total, 71 non-overlapping GIST patients were identified with a *PDGFRA* exon 18 mutation of whom 48 (69%) patients with a D842V-mutated GIST (Figure 1).

D842V-mutated GISTs

Over 90% of patients had local or locally advanced disease at registry entry. Twenty-two patients received systemic treatment with imatinib out of which 17 patients were treated with neo-adjuvant or palliative intent. All but one had measurable disease at the start of therapy, since this lesion was below the detection criteria for CT evaluation (Table 1). Two patients had PR (Figure 2). Three patients had SD, and 9 patients had PD as best response.

For 2 patients, no follow-up CT scans were available; one patient underwent resection shortly after the start of therapy and one patient had started therapy recently and was therefore not evaluable yet. Pathological response was evaluated in 7 out of 12 neo-adjuvant treated patients. None of these cases showed a good pathologic response (Table 2). Repeated molecular analyses in different parts of the tumor from the two patients showing PR confirmed a D842V mutation in all tumor regions.

Median follow-up time for all patients receiving imatinib with neo-adjuvant and palliative intent was 11 months (range 0-131). Out of 17 patients treated with neo-adjuvant and palliative intent, 10 patients showed PD. Median TTP was 8 months (range 0-42). Patients who progressed on imatinib showed a median TTP of 2.5 months (range 0-8). Five patients had died during follow-up, 3 due to disease progression.

Three out of 11 patients in the high-risk category received adjuvant treatment, and no patients showed recurrence in this group during median follow-up period of 23 months (range 1-84). Out of 8 high-risk patients who did not receive adjuvant treatment two had recurrence during the follow-up period.

Non-D842V mutated GISTs

Seventeen patients with a non-D842V mutated GIST had local or locally advanced disease at registry entry. Three patients received imatinib with neo-adjuvant intent and 5 with palliative intent, resulting in 8 non-D842V mutated GIST patients with measurable disease. Six patients had PR and two patients had SD as best response. Good pathologic response was seen in one patient harboring an I843_D846del mutation out of 2 patients who had pathologic evaluation. Table 2 describes all specific mutations in *PDGFRA* exon 18 in patients with measurable disease and their responses (Table 2).

Median follow-up time for patients receiving imatinib with neo-adjuvant or palliative intent was 24.5 months (range 3-132). Two patients had progression; one patient progressed within 7 months and the other patient progressed within 27 months.

Three out of the four high-risk patients received adjuvant treatment. One had recurrence after 1 year of adjuvant imatinib therapy. Two patients, who did not receive adjuvant treatment, also had recurrence. One of them had high-risk disease, the other had an unknown risk category.

Table 1: Patient characteristics.

Characteristics	Total (71)	D842V-mutated GISTs N = 48	Non-D842V mutated GISTs N = 23
Sex (male)	43 (60.6%)	28 (58.3%)	15 (65.2%)
Age in years (median; range)	58 (23-87)	56 (23-80)	62 (46-87)
Tumor status at registry			
Localized disease	48 (67.6%)	33 (68.8%)	15 (65.2%)
Locally advanced	13 (18.3%)	11 (22.9%)	2 (8.7%)
Metastasized	10 (14.1%)	4 (8.3%)	6 (26.1%)
Primary tumor location			
Gastric	65 (91.5%)	44 (91.7%)	21 (91.3%)
Oesophagus	1 (1.4%)	-	1 (4.3%)
Unknown/miscellaneous	5 (7.1%)	4 (8.3%)	1 (4.3%)
Primary tumor size in mm (median; range)	85 (7-310)	90 (12-310)	62 (7-260)
Histology			
Spindle cell	32 (45.1%)	26 (54.2%)	6 (26.1%)
Epitheloid	24 (33.8%)	12 (25.0%)	12 (52.2%)
Mixed	11 (15.5%)	7 (14.6%)	4 (17.4%)
Not reported	4 (5.6%)	3 (6.3%)	1 (4.3%)
Mitotic index (per 5mm^2)			
5	41 (57.7%)	31 (64.6%)	10 (43.5%)
>5	16 (22.5%)	10 (20.8%)	6 (26.1%)
Unknown	14 (19.7%)	7 (14.6%)	7 (30.4%)
Risk category[a]			
Low risk	35 (53.5%)	26 (60.4%)	9 (39.1%)
High risk	15 (14.1%)	11 (12.5%)	4 (17.4%)
Insufficient information	11 (18.3%)	7 (18.8%)	4 (17.4%)
NA[b]	10 (14.1%)	4 (8.3%)	6 (26.1%)
Surgery			
Yes	64 (90.1%)	43 (89.6%)	21 (91.3%)
No	7 (9.9%)	5 (10.4%)	2 (8.7%)
Imatinib treatment			
Yes	36 (47.9%)	22 (45.8%)	14(60.9%)
No	35(52.1%)	26(54.2%)	9(39.1%)
Treatment objective			
Neo-adjuvant	15 (18.3%)	12 (20.8%)	3 (13.0%)
Palliative	10 (14.1%)	5 (12.5%)	5 (17.4%)
Adjuvant	11 (18.3%)	5 (12.5%)	6 (30.4%)
No treatment	35 (49.3%)	25 (54.2%)	9 (39.1%)

GISTs: gastrointestinal stromal tumors
[a] Risk category according to Miettinen's criteria.
[b] Patients presented with metastatic disease, therefore no risk category is applicable.

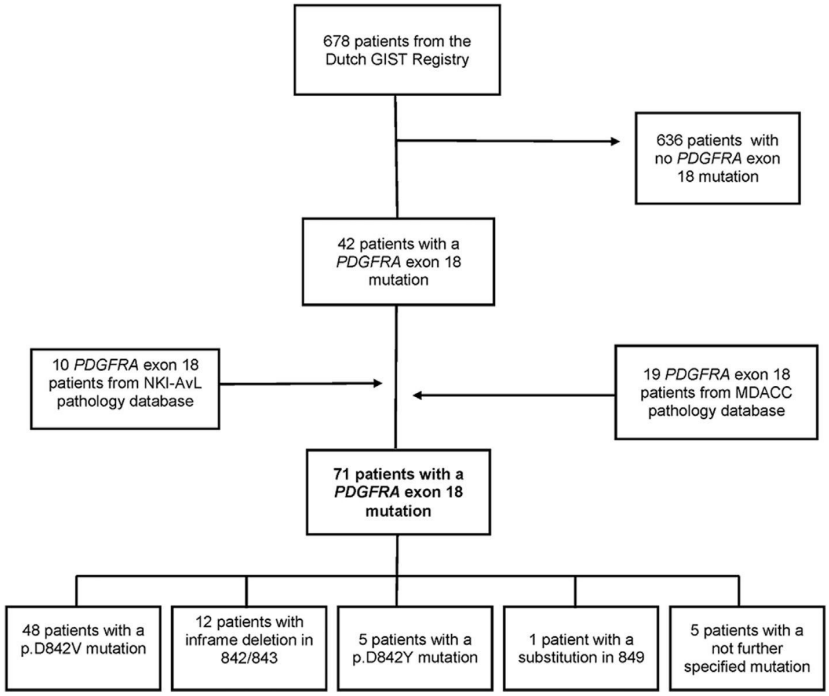

Figure 1: Flowchart describing inclusion of GIST patients with *PDGFRA* exon 18 mutations.

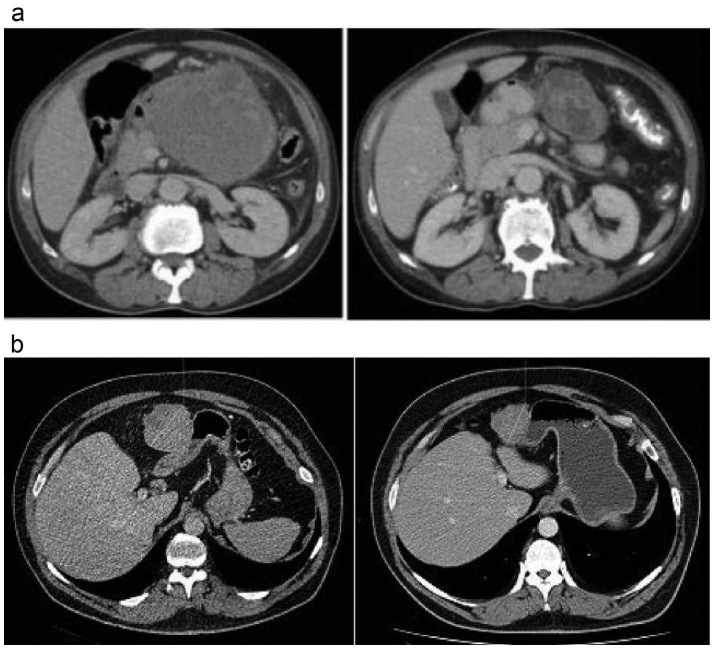

Figure 2: (A) Radiological response in a neo-adjuvant treated D842V-mutated GIST patient. (B) Radiological response in a D842V-mutated GIST patient treated with palliative intent.

Table 2: Radiological Choi responses and pathological responses in patients with measurable disease treated with palliative or neo-adjuvant intent.

***PDGFRA* exon 18 mutation type**	**Radiological responses**				**Pathological responses**				**Total***
	Partial response	**Stable disease**	**Progressive disease**	**No data**	**Good**	**Intermediate**	**None**	**No data**	
D842V	2 (12.5%)	3 (18.8%)	9 (56.3%)	2 (12.5%)	0 (0.0 %)	1 (6.3%)	6 (37.5%)	9 (56.3%)	16
Other exon 18 mutations	6 (75.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)	1(12.5%)	0 (0.0%)	1 (12.5%)	6 (75.0%)	8
p.D842_D846delinsG	0	1	0		0	0	0	1	
p.D842_H845del	1	0	0		0	0	0	1	
p.D842_N848del	1	0	0		0	0	1	0	
p.D842Y	1	0	0		0	0	0	1	
p.I843_D846del	1	0	0		1	0	0	0	
p.I843_S847delinsT	0	1	0		0	0	0	1	
p.Y849H	1	0	0		0	0	0	1	
Other mutations in exon 18 not further specified	1	0	0		0	0	0	1	

* Could only be assessed in patients treated with imatinib prior to surgery.

Discussion

We assessed responses to imatinib in GIST patients harboring a *PDGFRA* exon 18 mutation in a large observational cohort treated in routine clinical care. Interestingly, we showed that a small fraction of D842V-mutated GISTs respond to treatment with imatinib. One remains recurrence-free after neo-adjuvant treatment for almost 3 years and the other is progression-free during the 10 years of follow-up.

The response to imatinib in D842V-mutated GIST in our study contrasts the responses described in prior in vivo and in vitro studies. In these studies, D842V mutation has consistently shown to be imatinib-resistant.(5,6) In one study by Cassier et al. (2012), in vivo response was described in 32 D842V-mutated GISTs, showing no PR, 21 patients with PD and the rest with SD as the best response.(6) These findings are similar to those found in the study conducted by Corless et al., in 2005.(5) They found 35 patients in their study and 181 unique patients in total described in literature with a D842V mutation in exon 18. None of these patients showed response to imatinib. In these studies, response evaluations were conducted by RECIST. It is well known that response by Choi's criteria is correlated with TTP and that size-based response criteria may lead to an underestimation of the imatinib response in GIST.(12,13) However, the responses in the two D842V-mutated GIST patients in our study would have been classified as PR even by RECIST guidelines. Though no additional mutations were detected in our patient samples and repeated molecular analyses confirmed D842V mutation, one could speculate that heterogeneity within the tumor might have resulted in the responses noted in our patients.(14)

Similar to the earlier studies a large proportion of the D842V-mutated patients had PD as best response with a short TTP. This resistance to imatinib is thought to be the result of D842V mutation affecting the tyrosine kinase receptor activation loop. A D842V mutation in *PDGFRA* leads to reduced accessibility of the adenosine triphosphate (ATP) pocket and thereby to relative resistance to imatinib.(1) Corless et al. have found that other substitutions in codon 842, except for D842Y, also show resistance to imatinib.(5)

In line with prior studies we found that patients with a non-D842V mutated GIST respond well to imatinib. Despite the fact that the imatinib-resistant D842V mutation comprises a large majority of mutations in *PDGFRA* exon 18, approximately 30% have other mutations involving exon 18 of *PDGFRA* and all have shown favourable responses to imatinib.(5,15,16) Also, median TTP in our non-D842V mutated GIST patients with advanced disease was similar to other imatinib sensitive GIST patients.

International guidelines regarding adjuvant and neo-adjuvant treatment do not recommend imatinib for GIST patients harboring a D842V mutation.(9) It is therefore important to perform mutation analysis to determine the driver mutation and its sensitivity to imatinib. Interestingly, imatinib with neo-adjuvant and adjuvant intent was still frequently given in our cohort of D842-mutated GIST. It is possible that the mutation results were not available at the time of initiation of therapy. Nine D842V-mutated GIST

patients in our cohort were given adjuvant or neo-adjuvant treatment. Patients with *PDGFRA* exon 18 mutated GIST often have low mitotic activity and are considered to be low risk. Joensuu et al. showed that a mitotic count of over 5 per 50 high power field predicts for high risk for recurrence.(15) It is unknown whether with D842V-mutated GIST might benefit from adjuvant treatment. Although in our cohort slightly more recurrences occurred in non-treated patients with a high-risk tumor, no conclusions can be drawn considering the low patient numbers and heterogeneous follow-up time.

In case of a locally advanced tumor, the European Society for Medical Oncology (ESMO) guideline recommends resection without prior imatinib therapy in less sensitive tumors like D842V-mutated GISTs. Twelve of our patients with locally advanced GIST received imatinib and a quarter did not undergo surgery eventually. Again, it is unclear if the treating physician had the mutation data available at the time of treatment initiation.

For GIST patients harboring a D842V mutation with advanced disease no specific recommendations on treatment are described in international guidelines.(9,10) Given the known resistance to imatinib in D842V-mutated GIST, therapeutic alternatives are being investigated but proven therapies are still lacking.(17-20) Therefore, it was not a surprise to us that imatinib is still given in routine clinical care and this helped us evaluate the utility of imatinib in this population.

Patients in our study were treated in six different expert centers, resulting in a representative sample of patients. Evaluation of best response was confirmed by two independent radiologists according to Choi's criteria. No prior study has described in vivo pathologic response in *PDGFRA* exon 18 patients. Agaram et al. showed little to no correlation between radiological and pathological response in GIST patients.(21) There is however evidence that patients with good pathological response show better PFS and overall survival (OS).(22) In our cohort, only one patient with good radiological response to imatinib had good pathologic response. Further interpretation is limited due to small numbers.

Even though our sample size is small, considering the rarity of *PDGFRA* exon 18 mutated GISTs, this is the first and largest cohort to date of patients treated in routine clinical care described in the literature. Unlike what has previously been described we have found clinical and radiological responses in few patients with D842V-mutated GIST. Considering that GIST might be a multiclonal disease, one might argue that these patients could have had different clones within their tumors. Therefore, in our view imatinib treatment should not be universally denied in D842V-mutated GISTs who are not surgically resectable. Given the lack of alternative treatments in advanced disease, it may be worth while to start imatinib treatment in D842V-mutated GISTs with frequent response evaluations.

Disclosures

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Conflict of interest statement

None declared.

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Paragraph 2.3

Remarkable effects of imatinib in a family with young onset gastrointestinal stromal tumors and cutaneous hyperpigmentation associated with a germline *KIT*-Trp557Arg mutation: case report and literature overview

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Abstract

Gastrointestinal stromal tumors (GISTs) occur mostly sporadically. GISTs associated with a familial syndrome are very rare and are mostly wild type for *KIT* and platelet-derived growth factor alpha (*PDGFRA*). To date 35 kindreds and 8 individuals have been described with GISTs associated with germline KIT mutations. This is the third family described with a germline p.Trp557Arg mutation in exon 11 of the *KIT* gene. The effect of imatinib in patients harboring a germline KIT mutation has been rarely described. Moreover, in some studies imatinib treatment was withheld considering the lack of evidence for efficacy of this treatment in GIST patients harboring a germline *KIT* mutation. This paper describes a 52-year old patient with a de novo germline p.Trp557Arg mutation with multiple GISTs throughout the gastrointestinal tract and cutaneous hyperpigmentation. Imatinib treatment showed long-term regression of the GISTs and evident pathological response was seen after resection.

Remarkably, the hyperpigmentation of the skin also diminished during imatinib treatment. Genetic screening of the family revealed the same mutation in two daughters, both with similar cutaneous hyperpigmentation. One daughter, aged 23, was diagnosed with multiple small intestine GISTs, which were resected. She was treated with adjuvant imatinib which prompted rapid regression of the cutaneous hyperpigmentation. Imatinib treatment in GIST patients harboring a germline *KIT* mutation shows favorable and long-term responses in both the tumor and the phenotypical hyperpigmentation.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most com-mon mesenchymal tumors in the gastrointestinal tract. Median age of diagnosis is around 60 years.(1) GIST can occur anywhere in the gastrointestinal tract, but predominantly arises in the stomach and small intestine. In 85% an activating somatic mutation in the tyrosine kinase receptor *KIT* or platelet-derived growth factor alpha (*PDGFRA*) receptor is found.(2) In locally advanced and metastatic disease, imatinib, a selective *KIT* and *PDGFRA* inhibitor, is effective for almost 90% of patients with advanced disease.(1) In addition, adjuvant imatinib in patients with local disease and high risk of recurrence can improve progression-free survival (PFS) from 36 to 65.6%.(3, 4) However, efficacy of imatinib in GIST depends on the type of gain-of-function mutation and affected codon. GISTs harboring a mutation in *KIT* exon 11 are most common and have the highest benefit of imatinib. GISTs are mostly sporadic, but can also occur in patients with genetic predisposition. Familial GISTs are mostly related to syndromes such as neurofibromatosis type 1 (NF1) or the Carney–Stratakis syndrome, associated with a succinate dehydrogenase (SDH) deficiency. Familial GISTs associated with germline *KIT* or *PDGFRA* mutations on the other hand are very rare. Thirty-five families and eight individuals, with either a de novo mutation or unknown family history, with germline mutations in *KIT* or *PDGFRA* have been reported in literature.(5–28) To our best knowledge, this is the fourth paper describing patients with germline p.Trp557Arg mutation; prior to this paper two families and one individual with GIST associated with the same germline mutation were described.(5, 20, 29) With regard to the rarity of this syndrome, the effect of imatinib in GIST patients harboring a germline *KIT* mutation has not often been described.(7, 11, 30) In some studies imatinib was withheld considering the lack of evidence for favorable responses in these patients.(10) This paper describes the effects of imatinib on the GISTs and the cutaneous hyperpigmentation associated with this syndrome in two related GIST patients. Additionally, we give an overview of literature on the effect of imatinib in GIST patients harboring a germline *KIT* mutation.

Case 1

In 1999 a then 36-year-old woman with a long history of pain in the upper abdomen and weight loss underwent gastroscopy showing multiple gastric tumors. Explorative laparotomy was performed and widespread tumor localizations in the entire gastrointestinal tract were found. Curative resection was therefore deemed not possible. Histopathological examination on samples from the stomach, small bowel and appendix revealed CD117 and CD34 positive spindle cells and no mitotic activity was found. The diagnosis multifocal low grade gastrointestinal stromal tumor (GIST) was made and a wait-and-see policy was initiated with frequent follow-up. After two years, two GIST lesions in the small bowel and the stomach showed radiological apparent progression

in size. Imatinib mesylate was then recently approved for the treatment of GIST. Initiation of imatinib 400 mg resulted in rapid tumor regression, followed by long-lasting disease stability (Figure 1). Also, pigmentations of the skin, commenced at the age of 12 on the face, hands, and feet, diminished within 3 weeks of imatinib treatment. After 7 years of imatinib treatment, resection of the three remaining lesions (gastric, small bowel, and perirectal) with curative intent was performed. Histopathological analyses of the gastric lesion revealed merely calcification and fibrosis and no viable tumor. For the other lesions the diagnosis GIST without mitotic activity was confirmed. Treatment with imatinib was well tolerated for another 5 years. Follow-up computed tomography (CT) scans showed complete remission. Twelve years after initiation, imatinib treatment was discontinued. After 1 year of discontinuation of imatinib, recurrence of a GIST in the small bowel was seen. Imatinib was restarted and after 3 months a resection of a 13 mm lesion was performed. Morphologic features were consistent with low grade GIST. It is uncertain if this was a recurrence of a previous lesion or a new primary lesion. Given the earlier response to imatinib and the occurrence of a new lesion after imatinib discontinuation, lifelong imatinib therapy was agreed on. Fifteen months after resection, no evidence of disease was found. Considering the multi-localization of the disease, the young onset, and the depigmentation under imatinib treatment, mutational analyses was performed to explore the presence of a germline mutation. Family history was unremarkable. Mutational analyses in the patient's blood showed a heterozygous c.1669 T > C, p.Trp557Arg mutation in exon 11 of the *KIT* gene. The *KIT* gene was analyzed by polymerase chain reaction (PCR) and sequencing of both DNA strands of the entire coding region and the highly conserved exon–intron splice junctions. Neither of the patient's parents showed apparent pigmentations of the skin and molecular analyses on blood samples of both parents showed absence of the defect, indicating a de novo germline *KIT* mutation. At time of diagnosis, the patient had three under-aged healthy daughters. Considering their young age and the uncertainty of the implications and prognosis of a potential positive bearer status for germline *KIT*, a decision was made not to perform genetic analyses at that time and to wait-and-see until they reach adulthood.

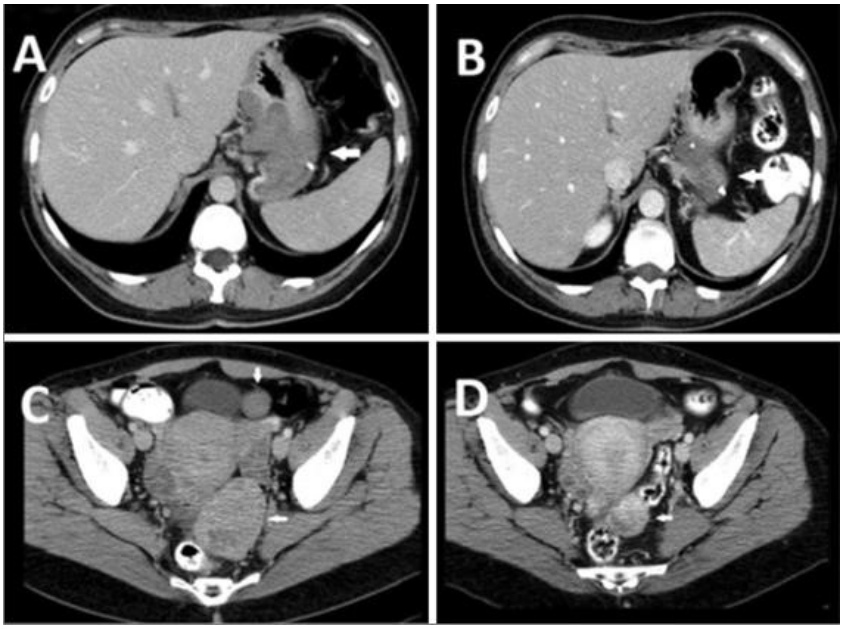

Figure 1: Both gastric lesions (A,B) and pararectal lesions (C,D) show apparent regression within 6 months after initiation of imatinib treatment.

Case 2

After reaching adulthood, the 23-year-old daughter of the patient in case 1 came to our clinic together with her two sisters, aged 22 and 19, for genetic testing. DNA sequencing analyses was conducted in two different DNA-isolations to test for the same germline *KIT* exon 11 mutation as the mother, c.1669T > C, p.Trp557Arg. Our 23-year-old patient and her 22-year-old sister tested positive (Figure 2). Both had prominent hyperpigmentation on the hands, feet, axilla, and groin, as well as friction-induced and trauma-induced pigmentation (Figure 3A). The histopathology of these pigmentations consisted of hyperpigmentation with normal melanocytes in morphology and number. Biannual screening by MRI enteroclysis was initiated and showed no tumor in the 22-year-old sibling. In our 23-year-old patient however, two adjacent small bowel lesions were found, 27 and 38 mm in diameter (Figure 4A). ^{18}F-flurodeoxyglucose (FDG)-positron emission tomography (PET) confirmed two FDG-active lesions and no other tumor activity in the abdomen (Figure 4B). Laparoscopic resection of the involved segment of the jejunum was performed. Histopathologic analyses revealed a 42 mm and a 39 mm spindle cell type lesion and up to one mitosis per 5 mm^2, consistent with low grade GIST. In the non-tumorous part of the jejunum near the myenteric plexus a profound segmental hyperplasia of the interstitial cells of Cajal was seen (Figure 5B, C). In a multidisciplinary meeting an indication for adjuvant treatment with imatinib 400 mg for at least 3 years was

agreed on. After 3 years a possible extension of this period will be discussed. This decision was based on the expected reoccurrence of GIST given the multilocalization of GIST, the germline *KIT* mutation, and morphologic precursor changes in the non-tumorous parts of the gastrointestinal tract. Similar to the mother, her pigmentations diminished and in general the skin tone and hair color seemed lighter within 3 months of imatinib treatment (Figure 3B). Imatinib toxicity was mild, including fatigue and grade 1 muscle cramps. After 15 months of treatment, no evidence of disease was found.

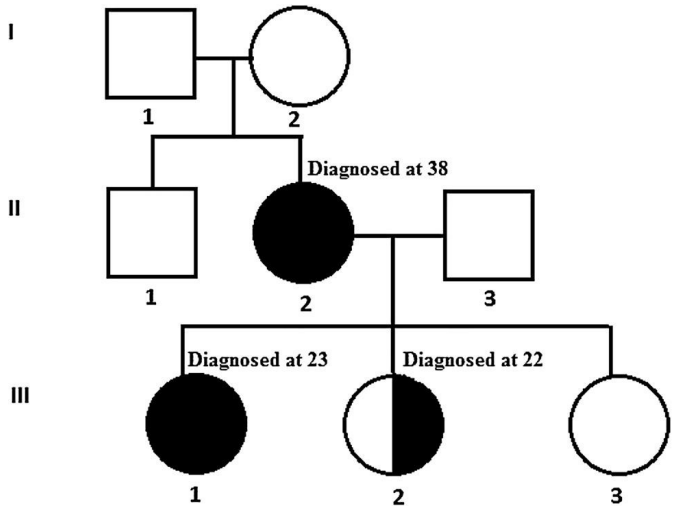

Figure 2: Pedigree of the family with age at time of diagnosis of the germline p.Trp557Arg mutation in *KIT* exon 11. Black symbols cases with mutation and GIST; black and white symbols cases with mutation but no GIST detected; squares males; circles females.

Figure 3: (A) Before initiation of imatinib mesylate there was apparent pigmentation on the hand, especially on the phalanges. (B) After 3 months of imatinib treatment the pigmentations diminished, and the overall skin tone became lighter.

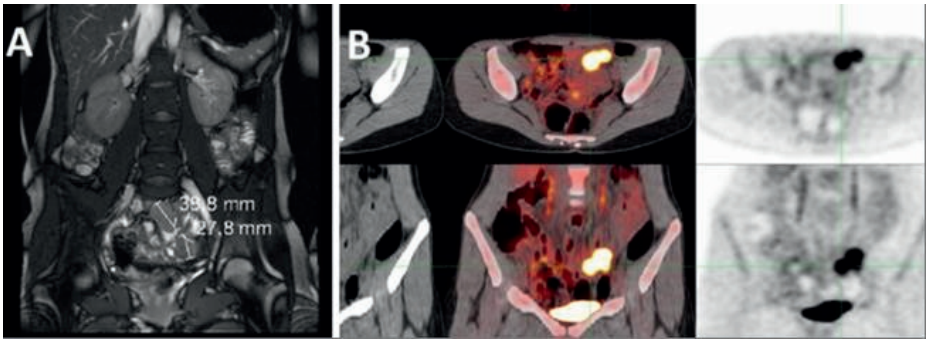

Figure 4: (A) Screening by MRI enteroclysis in our 23-year old patient showed two lesions (38 and 27 mm). (B) FDG-PET confirmed the presence of two active lesions and no other lesions were found.

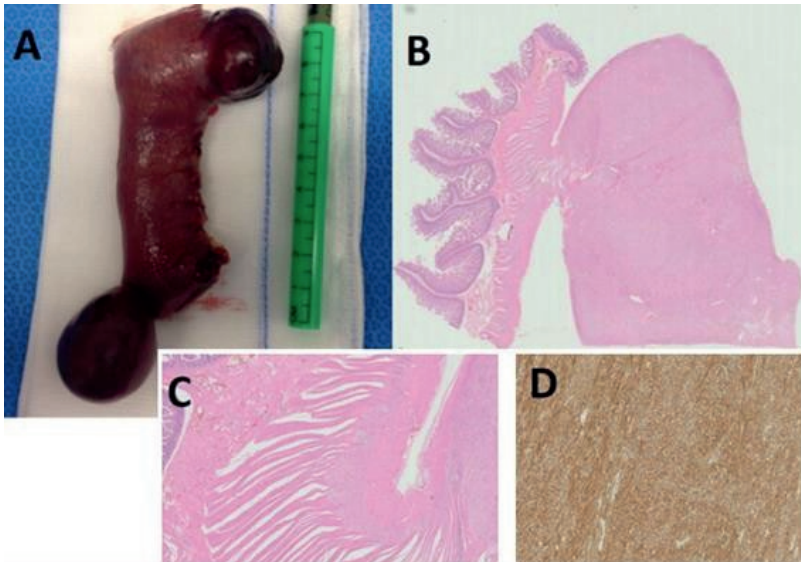

Figure 5: (A) Partial jejunum resection with the two GIST lesions in the 23-year-old patient described in case 2. (B) Hematoxylin and eosin (H&E) staining of part of the jejunum with the exophytic growing GIST (original magnification: ×20). (C) H&E stained close-up of the trajectory from the tumor to the non-tumoral part showing hyperpla-sia of the interstitial cells of Cajal (original magnification: ×40). (D) Immunohistochemical expression of DOG1 (original magnification: ×80).

Table 1: Patient characteristics.

Case	Type of mutation	Age of GIST diagnosis	Effect of imatinib on tumor	Effect of imatinib on cutaneous hyperpigmentation	Follow-up
Graham et al. [9]	*KIT* exon 13, p.Lys642Glu	56	SD	NA. Pre-existent vitiligo was unrelated	SD after 19 months
Campbell et al. [28]	*KIT* exon 11, unspecified	49	Not specified	Diminished within 3 months	2 years
Adela Avila et al. [27]	*KIT* exon 11, p. 559V > A	27, 30, 32, 35	Not specifically speci fied. 'progressive reduction of tumors'	Reduced melanosis	Unknown
Bamba et al. [5]	*KIT* exon 11, p.Val560del	43	CR and PR in most lesions	NA	1 year
Piqueres-Zubiaurre et al. [29]	*KIT* exon 11, p.Leu576Pro	Unknown (mother of 11-year old patient)	CR	Lightening of the skin	Unknown
Case 1, this paper	*KIT* exon 11, p.Trp557Arg	36	PR	Diminished within 2 weeks	NED after 13 years
Case 2, this paper	*KIT* exon 11, p.Trp557Arg	23	NA	Diminished within 3 weeks	NED after 15 months

[a] Univariate analyses using Chi-square test for categorical variables and Mann-Whitney U for continuous variables.

[b] Defined as GISTs needing neo-adjuvant imatinib treatment before surgery is deemed possible or safe.

Discussion

GISTs are mostly sporadic and GISTs associated with germline *KIT* mutations are very rare. Up until today 35 families and 8 individual patients have been described before, with various phenotypical characteristics. Patients were described to have pigmentation anomalies, urticarial pigmentosa, dysphagia, and/or mastocytosis. This paper describes the occurrence of GIST and hyperpigmentation in a family with a mother with de novo germline p.Trp557Arg mutation in the *KIT* exon 11 gene. We show a remarkable and long term effect of imatinib in the GISTs. In addition, in both cases there was a striking effect on the pigmentation anomalies of the skin. Within weeks of imatinib treatment these pigmentations diminished and it even seemed like the overall skin tone became lighter. This effect of imatinib in the skin is described three times before in a GIST patient with a germline *KIT* mutation (Table 1).(30–32) C-KIT and its ligand stem cell factor (SCF) are believed to regulate the development and survival of melanocytes. By introduction of a tyrosine kinase inhibitor such as imatinib, the function of c-KIT is altered and may be responsible for impaired pigment production.(31) In general, GISTs with a somatic mutation in exon 11 of the *KIT* gene are previously known to have exceptionally good responses in sporadic GISTs with a partial response rate of almost 84%.(33) This is the

sixth paper describing the in vivo effect of imatinib in patients with GIST associated with a germline mutation in *KIT* exon 11 (Table 1). Similar results have been described in a prior study with an elderly patient receiving half-dose of imatinib (200 mg/ day).(7) In vitro, one other study described good responses to imatinib and nolitinib in a GIST associated with a germline *KIT* exon 11 mutation.(34) In this patient an expectant policy was chosen rather than a tyrosine kinase inhibitor. Another study has described the effect of imatinib in a patient with multilocalized GIST associated with a germline *KIT* exon 13 mutation (11) (Table 1). After imatinib treatment some lesions showed regression while others showed stable disease. He had ongoing response after 19 months.

Prolonged imatinib treatment might be debatable, since GISTs harboring a somatic p.Trp557Arg substitution are known to have a relatively indolent behavior.(4) However, a prior study on a large kindred with p.Trp557Arg germline mutation described several family members requiring prolonged hospitalization and three members have died most probably as a result of disease progression.(20) In another case with this type of germline mutation a 52-year old patient died eventually of disease progression. At that time, no imatinib was available yet.(16)

In this paper, two out of three daughters harbored a germline *KIT* mutation and had, other than pigmentations, no symptoms. This is the first paper describing GISTs associated with a germline *KIT* mutation detected by screening. In line with earlier recommendations, we conducted MRI in both daughters, resulting in surgery and systemic treatment in one daughter.(6) It is unclear what the consequences of a wait-and-see approach would have been. In a similar study on a family with germline *KIT* exon 11 mutation imatinib was withheld given the lack of evidence for symptom reduction and prolonged survival in these patients.(10) However, considering the symptomatic and progressive behavior of the GISTs in the mother and the cases described in prior literature, we could not assume an indolent course. Therefore, regular screening and, in case of presence of disease, treatment with imatinib was agreed on. The other sibling with a germline *KIT* mutation was not treated with imatinib given the lack of evidence for efficacy of imatinib for prevention of GIST.

In conclusion, GISTs associated with germline *KIT* mutations are very rare. Up until today, little to no evidence for long-term introduction of imatinib has been provided. We showed that imatinib treatment in GIST patients harboring a germline *KIT* exon 11 mutation does induce favorable and long-term responses in both the tumor and the phenotypical hyperpigmentation associated with this syndrome. Imatinib treatment should therefore be considered in these patients.

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3

Chapter 3

Adverse events

Paragraph 3.1

Imatinib-induced agranulocytosis in patients with gastrointestinal stromal tumors

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Abstract

Agranulocytosis is a rare but serious side effect of imatinib in gastrointestinal stromal tumor (GIST) patients. Imatinib is an inhibitor of the proto-oncogene tyrosine kinase (c-KIT) and the first-line agent in patients with locally advanced and metastatic GIST. Little evidence is available on the management of this adverse event, and consensus-based guidelines are lacking. In this article, we describe 4 patients with agranulocytosis after starting imatinib. In addition, an overview of the available literature concerning the underlying mechanisms is given, and therapeutic strategies for overcoming this adverse event are discussed. In our experience it appears safe to restart imatinib after normalization of neutrophil count. In case of relapse of agranulocytosis, reintroduction combined with prednisolone, with treatment with granulocyte colony-stimulating factor or dose reduction can be considered

Introduction

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors originating from the gastrointestinal tract. Constitutive activation of KIT receptor tyrosine kinase plays a pivotal role in the pathogenesis of GIST. Imatinib (Glivec, Gleevec) is a selective tyrosine kinase inhibitor active against the proto-oncogene c-KIT (CD117), BCR-ABL (or Philadelphia chromosome in chronic myeloid leukemia) and platelet-derived growth factor receptor (PDGFR) tyrosine kinases. Currently, imatinib is the standard treatment in locally advanced and metastatic GIST patients. Furthermore, imatinib has been approved for patients with chronic myeloid leukemia (CML).

Overall, imatinib therapy is well tolerated. Common side effects are periorbital edema, nausea, diarrhea, muscle cramps, fatigue, and skin rash. Dose-dependent hematologic toxicity affecting all hematopoietic lineages to a variable degree is observed clinically, especially in imatinib-treated CML patients.(1) In GIST patients treated with imatinib grades 3–4, neutropenia is reported in 4.8% of all cases.(2) Nevertheless, imatinib-induced complete agranulocytosis (a neutrophil count less than 0.1 103/ mL) is thought to be a rare adverse event.(3) After a first episode of imatinib-induced agranulocytosis treating clinicians are often reluctant to restart this effective drug.

In this article we report 4 GIST patients with imatinib-induced agranulocytosis (Table 1). In addition, we give an overview of available literature regarding the possible underlying mechanisms and the different therapeutic strategies for overcoming this adverse event. Finally, we give our recommendations for treating imatinib-induced agranulocytosis.

Case Reports

Patient A, an 87-year-old man, presented with a large intra-abdominal tumor (7.0 6.5 cm) and pulmonary lesions. Biopsy of the abdominal mass showed a GIST (mitotic index, 4/10 HPF; *KIT* exon 11 mutated). His medical history included restless legs syndrome, gastro-esophageal reflux disease, and locally advanced prostate cancer (T3bN0M0) 1 year earlier, for which he was treated with radiotherapy and hormonal therapy. His medications included goserelin implant, tolterodine, tamsulosine, hydroquinine, pantoprazole, and acetaminophen. Baseline laboratory testing showed a decreased hemoglobin level (Hb, 10.3 g/dL; range, 14.0–17.5 g/dL); all other bone marrow and organ functions were normal. Treatment with imatinib at a dose of 400 mg daily was commenced. Five weeks later he was admitted to our hospital because of fever and hypotension (90/50 mmHg). Further physical examination was unremarkable. Laboratory testing showed an Hb of 9.2 g/dL, white blood cell count (WBC) of 8.3 x 10^3/mL (range: 4.0–10.5 x 10^3/mL) with a complete agranulocytosis (absolute neutrophil count (ANC) < 0.1 x10^3/mL; range: 1.8–7.2 x 10^3 /mL) and thrombocytopenia (119 x 10^3 /mL; range: 150–400 x 10^3 /mL). Imatinib was discontinued, and broad-spectrum antibiotics were initiated. As a possible contributing

factor to neutropenia, hydroquinine was stopped. Further investigation including urine analysis and culture, chest x-ray, and blood cultures did not reveal a source of infection. He was afebrile on the second day, and he was discharged from the hospital on the sixth day. Full neutrophil recovery was reached 10 days after imatinib discontinuation. Three weeks after discharge, imatinib was restarted (400 mg/day) with weekly monitoring of blood levels. Six weeks afterward, the ANC dropped to 0.5 x 10^3/mL. Imatinib was discontinued again, and now ANC normalized within 2 weeks (2.2 x 10^3/mL). Within 1 month, 400 mg imatinib once daily was restarted in combination with 10 mg prednisolone. After 3 months of prednisolone, the dose was decreased to 10 mg every other day and stopped a week later. Eight months later, agranulocytosis did not recur, and the patient remained progression-free.

Patient B, a 41-year-old woman, underwent incomplete surgical resection of a multinodular gastric GIST (7 cm, spindle cell type, c-KIT positive, mitotic index 0/50 HPF). At the time of diagnosis, metastases in the liver and intra-abdominal lymph nodes were present. Palliative imatinib treatment at a dose of 400 mg daily was commenced. Baseline laboratory testing revealed mild normocytic anemia (Hb: 11 g/dL; MCV: 81 mm^3), WBC 8.9 x 10^3/mL, and ANC 7.1 x 10^3/mL. One month after initiation of systemic treatment, she was admitted because of fever. Laboratory testing showed a microcytic anemia (Hb: 10.3 g/dL; MCV: 78 mm^3), WBC 1.9 x 10^3/mL, and ANC 0.17 x 10^3/mL. Two days later the ANC dropped below the detection threshold (0.05 x 10^3/mL). Imatinib was discontinued, and broad-spectrum antibiotics were started. Because of ongoing neutropenia on the fifth inpatient day, bone marrow examination was performed revealing impaired granulopoiesis. A maturation arrest of neutrophils in the myelocyte stadium was seen without any other abnormalities. In addition, "normal" bowel tissue and neutrophil granulocytes in blood were screened for *KIT* exon 11 mutations. No mutations could be demonstrated in these samples.

Granulocyte colony-stimulating factor (G-CSF; 300 mg daily) was given for 5 days, resulting in rapid normalization of the ANC (18.5 x 10^3/mL). Further investigation did not reveal a source of infection, and she was discharged with a good clinical condition. Repeated bone marrow examination 2 weeks after discharge was unremarkable. Imatinib was restarted at a dose of 300 mg daily. Two weeks later neutropenia recurred (ANC: 1.2 x 10^3/mL), and imatinib was discontinued. Full neutrophil recovery was reached 1 week later, and imatinib was restarted (300 mg). Routine laboratory tests in the following 3 months were normal. Then imatinib was stopped because of imatinib-induced hepatitis. No alternative treatment was started. Follow-up computed tomography (CT) scans showed no progression of the residual lesions in the last 11 years.

Patient C, a 45-year-old woman, was diagnosed with an abdominal tumor (8.1 x 7.9 cm) originating from the small bowel. Ultrasound-guided biopsy showed a wild-type GIST. Neoadjuvant treatment with imatinib (400 mg daily) was started. The patient was taking no other medication. Baseline laboratory testing was unremarkable. One month after

starting imatinib, she complained of fever, chills, and a sore throat. Laboratory testing showed a WBC of 3.1 x 10^3/mL and an ANC of <0.1 x 10^3/mL. Imatinib was promptly discontinued, and she was admitted for the administration of broad-spectrum antibiotics and G-CSF (filgrastim 1 x 300 mg). Within 2 days she clinically improved, the fever resolved, and the ANC rose to 0.6 x 10^3/mL. Response evaluation after 1 month showed progressive disease, and an R0 resection of the tumor was performed. Adjuvant imatinib treatment was not given.

Patient D, a 53-year-old man, was found to have a rectal mass during evaluation for rectal bleeding. Biopsy revealed a c-KIT-positive spindle cell wild-type GIST. Laboratory testing showed an Hb of 7.1 g/dL. Neo-adjuvant treatment with imatinib (400 mg daily) was started because of the close relationship of the tumor with the anal sphincter. During routine laboratory testing 1 month after the start of imatinib, an ANC of 0.1 x 10^3/ mL was detected, and imatinib was discontinued. Ten days later the ANC recovered to 3.7 x 10^3/mL, and imatinib was restarted at a dose of once-daily 300 mg. Neoadjuvant treatment with imatinib could be continued for 6 months in total without recurrence of agranulocytosis, CT scans after 3 and 6 months showed a partial response and stable disease, respectively, after which it was planned for the patient to have a resection.

Table 1: Summary of cases described in this article.

Patient	Imatinib Daily Dose	Time to Agranulocytosis	Intervention	Time to Recovery Agranulocytosis	Reintroduction of IM[a]	Recurrence[b]	Cancer-Related Outcome
A							
First episode	400 mg	5 weeks	Stopped until recovery	10 days	Yes	Yes	Progression-free after 8 months
Second episode	400 mg	6 weeks	Reintroduction with prednisolone	2 weeks	Yes	No	
B							
First episode	400 mg	1 month	G-CSF dose and reduction (300 mg)	10 days	Yes	Yes	IM stopped after 3 months due to hepatic toxicity. Progression-free after 11 years
Second episode	300 mg	2 weeks	Stopped until recovery	1 week	Yes	No	
C							
	400 mg	1 month	G-CSF	2 days	No	N/A	Early resection due to progression
D							
	400 mg	1 month	Dose reduction (300 mg)	10 days	Yes	No	Resection after 6 months of therapy

Discussion

Non-chemotherapy drug-induced agranulocytosis is a rare but potentially serious adverse event that is characterized by a decrease in the peripheral neutrophil count to less than 0.5 x 10^3/mL because of cytotoxic or immunogenic mechanisms. The most feared complication of severe neutropenia is the development of potentially lifethreatening infection. In 1 GIST patient, pulmonary tuberculosis secondary to grade 3 imatinib-induced neutropenia was described in 2005 by Takashima et al.(4) Imatinib is a selective tyrosine kinase inhibitor active against c-KIT (CD117), BCR-ABL, and PDGFR tyrosine kinases. Imatinib is approved for treatment of CML and GIST. Myelosuppression can occur at any time during imatinib therapy, but it usually begins within the first 2 to 4 weeks of treatment.(5) In our cases, neutropenia occurred within approximately 1 month after initiation of imatinib. The incidence of hematotoxicity in CML patients treated in the first months was previously described to be most predominant at the start of treatment and to decrease after 18 months.(6) Hematologic side effects are mainly dose-dependent, include all 3 lineages, and are reversible on cessation of treatment. However, 1 study comparing imatinib 400 mg daily with 800 mg daily found no difference in the incidence of neutropenia.(7) Whether the development of imatinib-induced agranulocytosis is related to drug exposure (imatinib drug levels) is unknown. In none of our 4 cases were imatinib drug levels measured. In the future, cases measuring imatinib drug level may provide further insight into the underlying mechanisms of imatinib-induced agranulocytosis.

For now it remains unclear which patients are at risk for developing hematologic toxicity. A low ANC and low hemoglobin concentration at the initiation of imatinib are potential risk factors.(8) The development of myelosuppression is particularly common in CML patients treated with imatinib. In these specific groups, grade 3–4 neutropenia (ANC 0.5–1.0 and <0.5 x 10^3/mL, respectively) was reported to occur in 35%–45% of patients who were treated with 400 mg daily.(9) In CML patients myelosuppression is expected because of suppression of the malignant clone by inhibiting the BCR-ABL.

Interestingly, myelosuppression is also seen in imatinib-treated GIST patients who are assumed to have an uncompromised bone marrow function. That imatinib can affect the function of normal, nonmalignant cells suggests that additional pathways are involved leading to myelosuppression.(6) The c-KIT proto-oncogene (CD117), which is targeted by imatinib, has been shown to be present in several cell types including normal hematopoietic stem cells.(10) However, in vitro studies showed that the inhibitory effect of imatinib on normal CD34þ progenitor cells is largely independent of c-KIT signaling. This suggests that other mechanisms might be involved in the inhibitory effect.(11) The exact mechanism by which imatinib induces its antiproliferative effect on normal CD34+ cells has yet to be clarified. In addition to BCR-ABL and c-KIT, imatinib also inhibits platelet-derived growth factor (PDGF) activity. PDGF has been demonstrated to be an effective cytokine for the ex vivo expansion of normal early stem and progenitor cells.(12) Inhibition of PDGF activity by imatinib can therefore also contribute to myelosuppression.

Significant myelosuppression results in treatment interruptions or dose reduction, which may compromise responses to imatinib. In the case of clear agranulocytosis, cessation of imatinib treatment remains crucial to avoid further hazardous exposure. In patient B, repeated bone marrow examination demonstrated impaired granulopoiesis with a maturation arrest of neutrophils in the myelocyte stadium, which was reversible on cessation of imatinib treatment. All our patients experienced full recovery of the neutrophil count only a few days after discontinuation of imatinib. This is in line with 1 case study on imatinib-induced agranulocytosis in a GIST patient describing agranulocytosis and severe skin rash, which both spontaneously recovered after cessation of therapy.(13)

Limited data are available about the risk of recurrent neutropenia when imatinib is readministered when ANC > 1.5 x 10^3/mL. Rechallenge with imatinib in a slightly reduced dose after agranulocytosis in patient D was uneventful, with normal ANC. Patients A and B experienced recurrence of the neutropenia after imatinib rechallenge. Patient A was able to continue imatinib treatment in combination with prednisolone therapy. Patient B could restart imatinib after the second episode without further hematologic toxicity. Administration of G-CSF in patients B and C might have accelerated neutrophil regeneration.(14) In patients with CML, G-CSF has been shown to be effective in overcoming imatinib-induced neutropenia.(4,15–17) In this way, recovery of neutrophil counts can even be achieved during uninterrupted imatinib therapy. Treatment with G-CSF in nonchemotherapy drug-induced agranulocytosis is associated with a lower median duration of neutropenia (8 days in treated patients vs 9 days in untreated patients, P = 0.015). In this report no significant association between decreased case-fatality rates and use of hematopoietic cell growth factors could be observed.(3) However, imatinib therapy was not included in this analysis, and to our best knowledge, G-CSF administration in imatinib-induced neutropenia in GIST patients has never been studied. It therefore remains questionable whether the use of expensive G-CSF results in a clinical significant benefit and is justified in the absence of severe infection.

Patient A was able to continue imatinib treatment in combination with prednisolone therapy. This strategy was not previously described in imatinib induced agranulocytosis. Considering the short period this treatment is given to the patient and its low cost, this option can be considered. However, one can argue that reintroduction without prednisolone might have been uneventful as well. Furthermore, no immunological response was seen in the patient's bone marrow. Therefore, any possible effect of corticosteroids is unclear. Patient B could restart imatinib after the second episode without further hematologic toxicity. In this case, imatinib was reintroduced in a decreased dose of 300 mg. This strategy was also used in a study describing 13 CML patients receiving G-CSF without discontinuation of imatinib.5 Hwang et al described a dose reduction to 100 mg in 1 GIST patient, without relapse of agranulocytosis or skin toxicity observed.(13) Despite dose reductions all patients in both reports showed response. In Table 2 a summary of

available studies on different treatment strategies for imatinib-induced agranulocytosis is given.

Based on the sparse literature and our, albeit limited, experience in these 4 cases, we propose recommendations for patients with GIST presenting with imatinib-induced agranulocytosis (Figure 1). At the first episode of agranulocytosis, we recommend cessation of imatinib treatment until full neutrophil recovery. When neutrophils are recovered, imatinib can be restarted at the same dose. If there is a relapse of imatinib-induced agranulocytosis, we recommend a rechallenge with dose reduction, or the use of either G-CSF or low-dose corticosteroids in combination with full-dose imatinib. In case of a second relapse or in case of life-threatening relapse, one can consider alternative therapy. This can consist of second-line tyrosine kinase, like sunitinib, or early planned surgery in case of neoadjuvant therapy.

Conclusion

Imatinib-induced agranulocytosis is a rare but potentially serious adverse event with life-threatening infection as the most feared complication. Imatinib is usually effective in locally advanced and metastatic GIST, and a rechallenge with imatinib should be considered after a first episode of agranulocytosis and full recovery of the neutrophil count. In our limited experience this appears a safe approach, with strict monitoring of the hemogram. The use of G-CSF or corticosteroids can be considered. Imatinib treatment should not routinely be withheld to GIST patients encountering a first episode of imatinib-induced agranulocytosis.

Table 2: Summary of available studies on different treatment strategies for imatinib-induced agranulocytosis.

Article	No. of Patients	Primary Disease	Imatinib Daily Dose	Time to Agranulocytosis	Intervention	Time to Recovery Agranulocytosis	Reintroduction of Iimatinib	Outcome
Heim 2003[16]	6	CML	400–600 mg	12–41 days (median, 28days)	G-CSF with continuation of imatinib	1–7 days (median, 6 days) with G-CSF 28–42 days (median, 28 days) before G-CSF	Yes, all patients	1 death (blast crisis)
Heim 2003[16]	3	CML	600 mg	Unknown	Stop imatinib until recovery	Not reported	Yes, 1 patient	2 blast crises 1 CHR but no CCR
Quintas 2004[15]	13	CML	400–800 mg	4–174 days (median 67 days)	G-CSF with continuation of imatinib and dose reduction to 300 mg	Within 21 days (43–144 days) with G-CSF 4–49 Days (median, 20 days) before G-CSF	Yes, all	All alive, all response to imatinib
Takashima 2005[4]	1	GIST	400 mg	5 months	Stop imatinib	Not reported	No	Died 1 year later due to progressive disease
Zaucha 2006[18]	1	CML	600 mg	1 month	G-CSF with continuation of imatinib	No recovery	No	Died of septic shock
Khouri 2008[5]	1	CML	400 mg	1 month	Stop imatinib, start G-CSF	Not reported	Not reported	Alive
Hwang 2009[17]	1	CML	400 mg	3 months	G-CSF 300 mg/day, twice weekly	1 week	Yes	Relapse agranulocytosis, bone marrow examination showed M. Kahler
Hwang 2010[13]	1	GIST	400 mg	3 months	Stop imatinib and wait for recovery	1 month	Yes, with reduced dose of 100 mg due to skin rash	Alive and partial response
Zhao 2011[19]	38	CML	400 mg	12 days in control group 10 days in Berbamine group	Berbamine in combi-nation with imatinib with-drawal	79 (29–132) days in control group 42 (28–88) days in Berbamine group (recovery to ANC >2.0 10^9/L)	Yes	Control: Recurrence of agranulocytosis in 10 of 19 patients CCR in 17 of 29 Berbamine: Recurrence of agranulocytosis in 3 of 16 patients CCR in 23 of 34

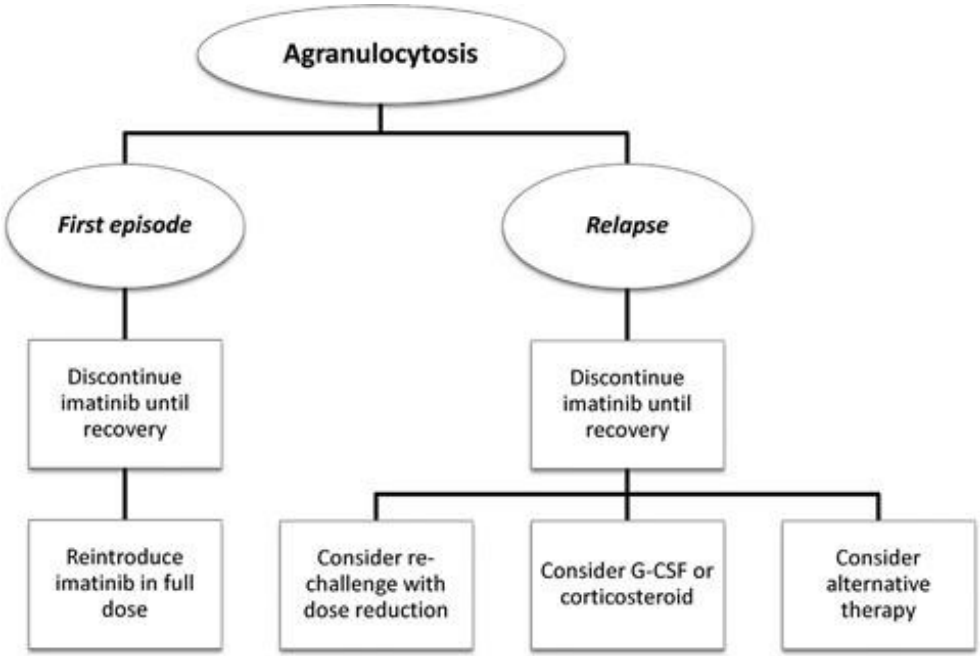

Figure 1: Recommendations for management of imatinib-induced agranulocytosis. When a patient presents with imatinib-induced agranulocytosis, we recommend stopping imatinib and waiting for full recovery. If the patient has a fever, broad-spectrum antibiotics should be administered. After full recovery, imatinib can be reintroduced at the same dose. In case of relapse of agranulocytosis, one should consider a rechallenge with imatinib in combination with dose reduction, granulocyte colony-stimulating factor (G-CSF), or low-dose corticosteroids, that is, prednisone 10 mg once daily. Prednisone dose can be slowly tapered with strict monitoring of the hemogram. One can also move to alternative therapy, for example, second-line therapy or surgery in the case of neoadjuvant therapy.

Declaration of Conflicting Interests

The first and second author equally contributed to the article. All authors listed sufficiently contributed to the article to be included as authors. There is no conflict of interest, financial or other.

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4

Chapter 4

Nuclear imaging

Paragraph 4.1

Early evaluation of response using ^{18}F-FDG PET influences management in gastrointestinal stromal tumor patients treated with neoadjuvant imatinib

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Abstract

Objective

^{18}F-FDG PET has previously been proven effective as an early way to evaluate the response of gastrointestinal stromal tumors (GISTs) to imatinib treatment. However, it is unclear whether early evaluation of response affects treatment decisions in GIST patients treated with neoadjuvant intent.

Methods

We retrospectively scored changes in management based on early evaluation of response by ^{18}F-FDG PET in patients in the Dutch GIST registry treated with neoadjuvant imatinib.

Results

Seventy ^{18}F-FDG PET scans were obtained for 63 GIST patients to evaluate for an early response to neoadjuvant imatinib. The scans led to a change in management in 27.1% of the patients. Change in management correlated strongly with lack of metabolic response ($P < 0.001$) and non–*KIT* exon 11–mutated GISTs ($P < 0.001$).

Conclusion

Performing ^{18}F-FDG PET for early evaluation of response often results in a change of management in GIST patients harboring the non–*KIT* exon 11 mutation and should be considered the standard of care in GIST patients treated with neoadjuvant intent.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors arising from the gastrointestinal tract. In local disease, surgery is the primary treatment of choice. In advanced GISTs, treatment with imatinib—a tyrosine kinase inhibitor that targets Bcr-ABL, c-KIT, and platelet-derived growth factor a (*PDGFRA*)—has resulted in spectacular responses. Depending on the type of driver mutation, the partial response rate is up to 84% (in the case of a mutation in *KIT* exon 11).(1,2) When complete resection is not feasible or would result in serious morbidity, neoadjuvant treatment with imatinib is advised until maximum response is achieved.(3,4) Whereas a volume response measurable by CT often requires 6–9 months of imatinib treatment, previous studies have shown that a metabolic response measured by ^{18}F-FDG PET can already predict imatinib responses within 1–8 d.(5–7) International guidelines therefore recommend early evaluation of response using ^{18}F-FDG PET in GIST patients treated with neoadjuvant intent.(3) By this means, patients without a metabolic response can be referred directly to surgery within 1–2 wk. Early evaluation by ^{18}F-FDG PET hence offers an opportunity to adjust and optimize treatment strategies in GIST patients treated with neoadjuvant intent. We aimed to assess to what extent management of these patients in clinical practice is influenced by the findings of ^{18}F-FDG PET.

Methods

^{18}F-FDG PET/CT scans obtained for patients in the Dutch GIST Registry were evaluated. The registry includes all patients diagnosed with GIST between January 2009 and October 2016 in the 5 GIST centers in The Netherlands: Netherlands Cancer Institute–Antoni van Leeuwenhoek, Leiden University Medical Center, Erasmus University Medical Center, Radboud University Medical Center Nijmegen, and University Medical Center Groningen. Data acquisition was approved by the local independent ethics committees and was in accordance with the Declaration of Helsinki.

The analysis included the ^{18}F-FDG PET scans of patients treated with imatinib with neoadjuvant intent. Early evaluation of response is defined as an evaluation within 8 weeks after the initiation of medical treatment or a change in its dose or type. Change in management was defined as a difference between the pre-PET and post-PET treatment strategies. Four categories of management change were defined: change in surgical management (e.g., surgery performed, postponed, or cancelled), change in systemic treatment (e.g., stopping, switching, or changing the dose), change in treatment objective (e.g., from curative to palliative), and change in management regarding a secondary tumor (e.g., diagnosis, resection, or treatment of a second tumor based on a PET result). Responses were derived from radiologic reports and, in general, were qualitatively categorized as complete, partial, or none.

Demographic and biologic characteristics such as sex, age, tumor size, tumor location, and tumor mutation status were derived from the Dutch GIST Registry. Statistical analyses were conducted using IBM SPSS Statistics 23. To assess an association between change in management and demographic and biologic characteristics, Pearson Chi-square (x^2) analyses were used for categoric variables and Mann–Whitney U tests were used for continuous variables. All tests were 2-sided, and a p-value of less than 0.05 was considered significant.

Results

Of the 781 patients in the database, 259 underwent ^{18}F-FDG PET—a total of 404 scans, of which 234 were obtained at base-line. Of the 170 PET scans obtained for treatment evaluation, 70 scans in 63 patients treated with neoadjuvant intent were considered to have been obtained for early evaluation of response. This number corresponds to 31% of the 202 patients in the database who had been treated with neoadjuvant intent. In all patients, treatment began with imatinib: 400 mg in 60 patients and 800 mg in 3 patients with *KIT* exon 9–mutated GIST. The patient characteristics are described in Table 1.

A metabolic response was seen in about 70% of PET scans, and a change in management in 27% (Table 2). A change in management correlated strongly with a lack of metabolic response (Pearson x^2, $p < 0.001$) and harboring of a mutation outside *KIT* exon 11 (Pearson x^2, $p < 0.001$) (Figure 1). Also, mutational status and response correlated strongly with each other (Pearson x^2, $p < 0.001$). Of 29 PET scans of GISTs with a non–*KIT* exon 11 mutation, 15 (52%) led to a change in management: 2 of 2 scans for *KIT* exon 13, 3 of 5 for *PDGFRA* 18, 4 of 7 for *KIT* and *PDGFRA* wild-type, and 6 of 12 for GISTs with an unknown mutation. No change in management was seen in the 3 patients with a KIT exon 9 mutation. For *KIT* exon 11–mutated GISTs, a change was seen in 3 of 41 scans (7%).

Of the 15 PET results that led to a change in management in non–*KIT* exon 11–mutated GISTs, a change in surgical management was seen once (3%), a change in systemic treatment was seen 6 times (21%; 3 regarding a switch to sunitinib and 3 regarding dose), both a change in dose and early planned surgery were seen 7 times (24%), and a second tumor necessitating treatment adaptation was seen once (3%). Three of the 41 PET scans of *KIT* exon 11 GIST patients led to a change in management: 2 times, the change involved systemic treatment (a dose increase after persistence of metabolic activity in parts of the tumor), and once, the change was due to discovery of a second primary tumor. No change in treatment objective was seen.

Change in systemic treatment led to improved metabolic response 2 times: once in a *KIT* exon 11–mutated GIST and once in a GIST with an unknown mutation. Early surgery resulted in R0 resections in 5 of 8 patients, and 1 patient had an R1 resection with ongoing disease-free survival at 61 months of follow-up. Peri-operative metastatic disease was revealed in 2 patients: 1 patient with wild-type GIST died of disease progression, and

1 patient with *PDGFRA* exon 18 (non-D842V) underwent debulking surgery with ongoing disease-free survival under imatinib treatment.

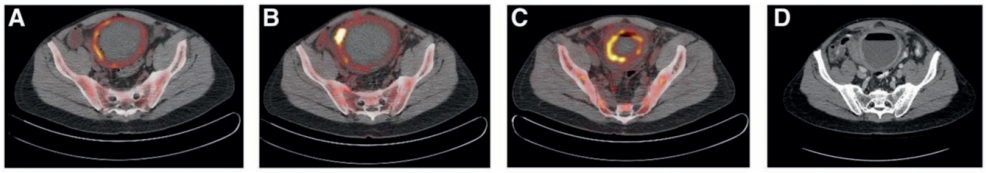

Figure 1: ^{18}F-FDG PET/CT in GIST patient with *KIT* exon 13 mutation.

(A) Baseline PET/CT image (SUV_{max} = 4.3). (B) PET/CT image after 2 weeks of treatment, showing both metabolic progression (SUV_{max} = 6.7) and size progression. Imatinib dose was increased from 400 to 800 mg daily. (C) PET/ CT image 4 weeks after increase of dose, showing notable response in size. However, because of persisting metabolic activity (SUV_{max} = 4.4) and increased symptomatology, early resection of tumor was performed. (D) CT image showing notable response in size after dose increase. R0 resection was performed, resulting in ongoing disease-free survival.

Table 1: Patient and tumor characteristics.

Characteristic	**Patients (*n* = 63)**
Sex	
Male	40 (63.5%)
Female	23 (36.5%)
Median age (y)	61 (range, 15–87)
Location of primary tumor	
Stomach	46(73.0%)
Small bowel	6(9.5%)
Duodenum	5(7.9%)
Rectum	5(7.9%)
Esophagus	1(1.6%)
Median primary tumor size (mm)	106 (range, 19–300)
Mitotic index	
>5 per 5 mm^2	40 (63.5%)
<5 per 5 mm^2	13 (20.6%)
Not reported	10 (15.9%)
Mutation status	
KIT exon 11	41 (65.1%)
KIT exon 9	2 (3.2%)
KIT exon 13	1 (1.6%)
PDGFRA exon 18	5 (7.9%)
Wild-type	7 (11.1%)
Not determined	7 (11.1%)

Table 2: ^{18}F-FDG PET/CT results before and after neoadjuvant imatinib treatment and resulting changes in management.

Result/change	**PET/CTs (*n* = 70)**
Baseline PET available?	
Yes, ^{18}F-FDG–avid	64 (91.4%)
Yes, not ^{18}F-FDG–avid	3(4.3%)
No	3 (4.3%)
Baseline resulted in change in management?	
Yes, change in treatment objective	3 (4.3%)
Yes, change regarding second tumor	3 (4.3%)
No change in management	61 (87.1%)
No baseline available	3 (4.3%)
Metabolic response?	
Yes, complete	20 (28.6%)
Yes, partial	30 (42.9%)
No	14 (20.0%)
No baseline available or no ^{18}F-FDG avidity at baseline	6 (8.6%)
Change in management (any)?	
Yes	18 (27.1%)
No	52 (72.9%)
Change in surgical management?	
Yes	8 (11.4%)
No	62 (88.6%)
Change in systemic treatment?	
Yes	15 (21.4%)
No	55 (78.6%)
Change in treatment objective?	
Yes	0 (0%)
No	70 (100%)
Change regarding second tumor?	
Yes	2 (2.9%)
No	68 (97.1%)

Discussion

Previous studies have shown that ^{18}F-FDG PET is a sensitive method of evaluating early response to treatment with tyrosine kinase inhibitors in GIST patients.(8–11) International guidelines recommend early assessment of response using ^{18}F-FDG PET in patients treated with neoadjuvant intent to prevent delay of surgery.(3) Also, early evaluation using ^{18}F-FDG PET is thought to optimize individual treatment.(5) However, to our knowledge, no study has assessed the actual influence of ^{18}F-FDG PET on treatment strategies. We showed that in 27% of cases, ^{18}F-FDG PET led to a change of management in GIST patients treated with neoadjuvant imatinib.

In GIST patients harboring a mutation other than *KIT* exon 11, a change in management was seen in over half the cases. Early assessment of response led to surgery with curative intent in all patients. However, 2 patients had perioperative metastatic disease that was not seen on either CT or ^{18}F-FDG PET. In all but 1 case, early surgery led to ongoing disease-free survival, implying that early evaluation by ^{18}F-FDG PET prevented progressive and unresectable disease. However, the retrospective nature of this study and the heterogeneous follow-up times are a major limitation to further interpretation of these results. In addition, the responses were evaluated by different nuclear physicians, potentially causing heterogeneous definitions of response.

Conclusion

In this nationwide series of imatinib-treated GIST patients harboring non–*KIT* exon 11 mutations, ^{18}F-FDG PET scans obtained for early evaluation of response in the neoadjuvant setting resulted in a change in management in half the cases. We therefore recommend that evaluation with ^{18}F-FDG PET be considered in this curative setting.

Disclosure

A research grant for the Dutch GIST Registry was received from Novartis, Pfizer, and Bayer. No other potential conflict of interest relevant to this article was reported.

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Paragraph 4.2

Early response evaluations by ^{18}F-FDG-PET/CT do not influence the management of patients with metastatic gastrointestinal stromal tumors (GIST) treated with palliative intent

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Submitted

Abstract

Objective

The aim of this study was to investigate the impact of ^{18}F-FDG-PET/CT on treatment decision making in metastatic gastrointestinal stromal tumor (GIST) patients.

Methods

This study retrospectively evaluated ^{18}F-FDG-PET/CT scans to monitor response of metastatic GIST patients treated with palliative intent. Data from the Dutch GIST Registry was used. Early scans (<10 weeks after start of treatment) and late scans (>10 weeks after start of treatment) were scored on the impact in change of treatment.

Results

Sixty-one PET/CT scans were performed for treatment evaluation in 39 patients with metastatic GIST of which 36 were early scans and 25 were late scans. Early PET/CT scans led to a change in management in 5.6% of patients and late PET/CT scans led to a change in management in 56% of patients.

Conclusion

In patients with metastatic GIST, early response evaluation using ^{18}F-FDG-PET/CT is not recommended.

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. GIST mainly occurs in elderly patients of both sexes and has an estimated incidence of 1-2 per 100.000 per year.(1) Metastatic or unresectable disease is described in 10 to 30% of patients with GIST.(2)

In metastatic GIST, systemic treatment with imatinib is the primary choice of treatment. Imatinib is a tyrosine kinase inhibitor that targets Bcr-ABL, c-KIT and PDGFRA. Since the introduction of imatinib, the survival of patients with GIST has improved significantly. The median overall survival of patients with advanced disease improved from 18 months to 5-6 years.(3-5) Treatment with imatinib leads to disease control in 70-85% of patients with advanced GIST with activating mutations in *KIT* exon 11, which is the most frequent site of mutation.(3) Treatment response monitoring is often performed using size and density measurements on CT scan.(6,7) Previous studies have shown that metabolic response measured by ^{18}F-FDG-PET/CT could predict imatinib responses within 1-8 days.(6-9) In patients treated with neo-adjuvant intent, ^{18}F-FDG-PET/CT has shown to change treatment in over half of patients.(10) Up until today no studies have been conducted assessing the influence of early response evaluation using ^{18}F-FDG-PET/CT in metastatic GIST patients. The aim of this study was to investigate the impact of ^{18}F-FDG-PET/CT on treatment decisions in GIST patients treated with palliative intent.

Methods

All GIST patients treated with palliative intent who were entered in the Dutch GIST Registry (DGR) and underwent an ^{18}F-FDG-PET/CT were included in this study. The DGR includes data of all GIST patients diagnosed since January 2009 in the 5 GIST centers in the Netherlands. These centers include the Netherlands Cancer Institute – Antoni van Leeuwenhoek, Erasmus University Medical Center, Leiden University Medical Center, University Medical Center Groningen and Radboud University Medical Center Nijmegen. Data acquisition was approved by the local independent ethics committees and was conducted in accordance with the Declaration of Helsinki. Data cut-off date was September 2017.

Patient and tumor characteristics were derived from the DGR. Baseline and response ^{18}F-FDG-PET/CT scans of metastatic GIST patients were evaluated and change in treatment was determined by assessing patients' medical records. Metabolic responders were defined as all patients with partial or complete metabolic response on ^{18}F-FDG-PET/CT, non-responders were defined as all patients with no response.

Change in treatment was defined as a switch in treatment strategy directly influenced by ^{18}F-FDG-PET/CT results and was divided in two categories: 1) change in surgical

treatment (e.g. surgery cancelled or change in surgical approach); 2) change in systemic treatment (change in dose, switch or stop systemic treatment).

The treatment evaluation scans were divided in two categories: early response scans and late response scans, with a cut off of 10 weeks after start of treatment. This cut off was based on the fact that response monitoring by CT in the majority of cases is performed approximately 10 weeks after start of treatment.

Two investigators (SF, MH) independently determined whether the reports of the ^{18}F-FDG-PET performed for response monitoring led to a change in management. Discrepancies were solved by consensus.

Statistical analyses were performed using IBM SPSS Statistics. Associations between change in management, the timing and results of ^{18}F-FDG-PET/CT and demographic and biological characteristics were assessed using Chi-square analyses for categorical variables and Mann-Whitney U for continuous variables. Kaplan Meier Estimates for Progression Free Survival were generated, stratified on metabolic responders and non-responders. Progression free survival was calculated from the date of start of systemic treatment until the date of progression, defined as the date on which treatment stopped due to disease progression. A p-value of <0.05 was considered statistically significant.

Results

In total, 888 GIST patients were entered in the DGR-database. Two hundred and twenty-one patients had metastatic disease. In total 105 ^{18}F-FDG-PET/CT scans were performed in 60 metastatic GIST patients. Eventually, 61 ^{18}F-FDG-PET/CTs were performed for response evaluation in 39 patients. (Figure 1) Patient characteristics of all 39 patients are described in Table 1.

Table 1: Patient Characteristics.

Characteristic	**Patients (*n*= 39)**
Sex	
Male	24 (61.5%)
Female	15 (38.4%)
Age in years (median; range)	69 (33-85)
Location primary tumor	
Gastric	21 (53.8%)
Small bowel	12 (30.8%)
Duodenal	2 (5.1%)
Colon	2 (5.1%)
Other	2 (5.1%)
Mutation status	
KIT exon 11	29 (74.4%)
KIT exon 9	2 (5.1%)
KIT exon 13	1 (2.6%)
KIT exon 17	1 (2.6%)
PDGRFA exon 18	1 (2.6%)
PDGRFA exon 12	1 (2.6%)
Unknown	4 (10.2%)
Secondary mutations	
Not reported/undetected	36 (92.3%)
Present	3 (7.7%)
Baseline Comorbidity - Charlson index score	
<4	33 (84.6%)
≥4	5 (12.8%)
Unknown	1 (2.6%)
Baseline PET available?	
Yes, FDG-avid	37 (94.9%)
Yes, but not FDG-avid	0 (0.0%)
No baseline available	2 (5.1%)

Patients received first line imatinib treatment in 52 out of 61 response evaluation scans (85.2%), second line sunitinib treatment in 6 scans (9.8%) and third line treatment (once with regorafenib and twice with nilotinib) in 3 scans (4.9%). In 36 out of 61 response scans (59%) a metabolic response was detected.

In total, 16 out of 61 (26%) ^{18}F-FDG-PET/CT scans led to change in management. Eleven out of 16 ^{18}F-FDG-PET/CT scans were performed directly after the diagnostic CT in order to clarify the indeterminate results of the CT. This involved a metabolic evaluation of possible progression seen on CT. The other five ^{18}F-FDG-PET/CT scans were performed to assess whether metabolic progression is seen in one or more lesions prior to surgery or switch in systemic treatment.

Thirty-six early response PET scans were performed with a median of 24 days after start of or change in systemic treatment (range 3-70, SD 18.7). 25 late response PET scans were performed with a median of 293 days after start of or change in systemic treatment (range 80-1212, SD 332). Metabolic response was detected in 28 early response scans (80%) and in 8 late response scans (33.3%).(Table 2)

Table 2: ^{18}F-FDG-PET/CT outcomes in 39 patients with response evaluation.

^{18}F-FDG-PET/CT outcomes	**Total n=61**	**Early response evaluation (n=36)**	**Late response evaluation (n=25)**
Metabolic response?			
Yes, complete response	16 (26.2%)	14 (38.9%)	2 (8%)
Yes, partial response	20 (32.8%)	14 (38.9%)	6 (24%)
No response	23 (37.7%)	7 (19.4%)	16 (64%)
No baseline available	2 (3.3%)	1 (2.8%)	1 (4%)
Response PET resulting in any change of management?			
Yes	16 (26.2%)	2 (5.6%)	14 (56%)
No	45 (73.8%)	34 (94.4%)	11 (44%)
Response PET resulting in a change in surgical treatment?			
Yes	10 (16.4%)	1 (2.8%)	9 (36%)
No	51 (83.6%)	35 (97.2%)	16 (64%)
Response PET resulting in a change in systemic treatment?			
Yes	6 (9.8%)	1 (2.8%)	5 (20%)
No	55 (90.2%)	35 (97.2%)	20 (80%)
Systemic treatment			
First line treatment	52 (85.2%)	32 (88.9%)	20 (80%)
Second line treatment	6 (9.8%)	2 (5.6%)	4 (16%)
Third line treatment	3 (4.9%)	2 (5.6%)	1 (4%)
Response PET performed after start of treatment (days)			
Median (range)	57 (3-1123)	24 (3-70)	293 (80-1212)

Out of 36 early response ^{18}F-FDG-PET/CTs (Figure 2), two scans led to a change in management (5.6%), while 14 out of 25 (56%) late response ^{18}F-FDG-PET/CTs led to a change in management. Late response ^{18}F-FDG-PET/CTs and lack of metabolic response were strongly correlated with change in management ($p < 0.001$ and $p=0.002$ respectively). One early scan led to a change in surgical management, concerning a cancellation of planned surgery due to unexpected progression in multiple lesions. The other ^{18}F-FDG-PET/CT scan led to a change in systemic treatment (switch from imatinib to sunitinib). Nine late ^{18}F-FDG-PET/CT scans led to a change in surgical management. In these 9 scans progression of a solitary metastasis was observed, which led to metastasectomy. The results of 5 late scans led to a change in systemic management, three of these scans led to an increase in dose and two scans led to a switch to sunitinib (Figure 3).

Survival analyses showed no significant difference in progression-free survival between responders and non-responders, with median PFS of 273 weeks (95% confidence interval (95% CI) 237-308 weeks) and 260 weeks (95% CI 135-384 weeks) respectively ($p=0.779$).

Discussion

In this study, we investigated the influence of ^{18}F-FDG-PET/CT on treatment strategies in patients with metastatic GIST. This is to our best knowledge the first study to assess the actual impact of this imaging technique on treatment decisions in metastatic GIST. Prior studies have suggested that early response evaluation using ^{18}F-FDG-PET/CT might have a significant impact on treatment changes in metastatic GIST.(10-16) One study has found a significant impact of ^{18}F-FDG-PET/CT in the management of neoadjuvant treated GIST patients.(10) In our current restrospective analysis in metastatic GIST, almost 95% of early response scans have not led to a change in management, whereas the late response scans led to a change in management in over half of the scans (56%).

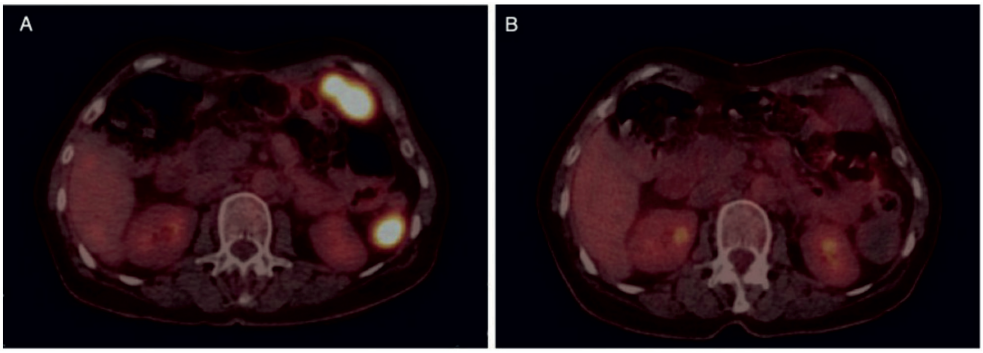

Figure 2: (A) Baseline ^{18}F-FDG-PET/CT of a GIST patient with a KIT exon 11 mutation. (B) Complete metabolic response 2 weeks after start of imatinib 400 mg daily.

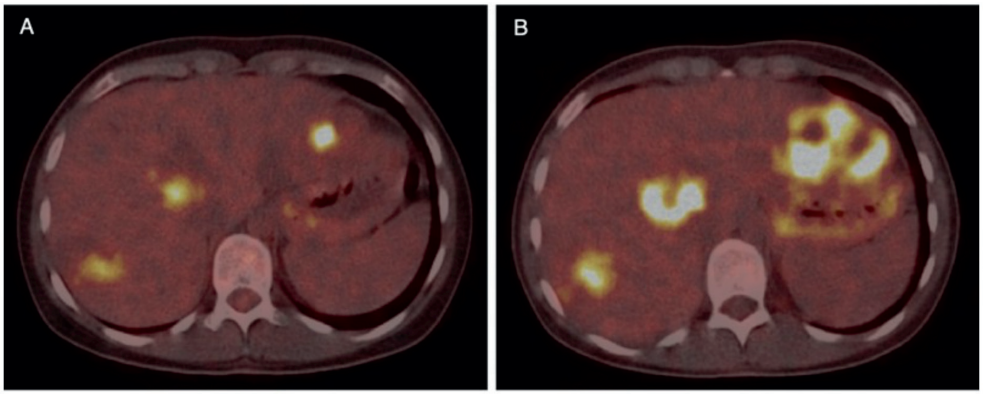

Figure 3: (A) ^{18}F-FDG-PET/CT of a GIST patient with a KIT exon 11 mutation, after 3 weeks of treatment with imatinib 800 mg. (B) Metabolic progression observed after 7 months of treatment with imatinib 800 mg daily, resulting in change of systemic treatment to sunitinib 37.5 mg daily.

Change in management was mainly a result of non-response or progression. Change in management was mostly surgical and resulted in 36% of the cases in a metastasectomy. Interestingly, no difference in PFS was found between non-responders and responders. This suggests that change in management in non-responders might have been effective.

Our results hence suggest that conducting an ^{18}F-FDG-PET/CT scan later in treatment might result in prolonged first line treatment with imatinib. However, considering the retrospective nature of this study, it is reasonable to assume that these outcomes can be a result of selection bias. In our current daily clinical practice, we do not routinely perform ^{18}F-FDG-PET-CT in metastatic GIST patients and based on our findings we would not recommend this.

In conclusion, in contrast to previous studies suggesting a significant impact on ^{18}F-FDG-PET/CT in patients with metastatic GIST, early response evaluation using ^{18}F-FDG-PET/CT does not influence treatment decisions in these patients. ^{18}F-FDG-PET/CT can be useful in case of indeterminate CT results or when for specific predefined indications a response evaluation is needed later in treatment.

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5

Chapter 5

Pharmacokinetics in GIST

Paragraph 5.1

Imatinib pharmacokinetics in a large observational cohort of gastrointestinal stromal tumor patients

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Abstract

Background

Low trough imatinib concentration (C_{min}) values have been associated with poor clinical outcomes in gastrointestinal stromal tumor (GIST) patients. This study describes the pharmacokinetics of imatinib in a large cohort of GIST patients in routine clinical care.

Methods

An observational study was performed in imatinib-treated GIST patients. Patient and tumor characteristics were derived from the Dutch GIST Registry and medical records. Imatinib concentrations were measured by liquid chromatography with tandem mass spectrometry. The analyses included the occurrence of a low imatinib C_{min} (<1000 µg/L), the change in the C_{min} over time and the correlation between exposure and response.

Results

In total, 421 plasma samples were available from 108 GIST patients. Most patients (79.6 %) received an imatinib dose of 400 mg. The inter- and intrapatient variabilities in C_{min} were 54 and 23 %, respectively. In the first steady-state sample, 44.4 % of patients presented with C_{min} values <1000 µg/L; 32.4 % of patients had values <1000 µg/L in >75 % of their samples. Only 33.3 % of patients had C_{min} values ≥1000 µg/L in all measured samples. No decrease in C_{min} over time was found ($P < 0.05$). Fifty-seven (91.9 %) of 62 palliative-treated patients had a tumor response (median C_{min} 1271 µg/L). Five palliative patients (8.1 %) did not respond (median C_{min} 920 µg/L). Given the limited number of non-responders in this cohort, no statistically significant association with clinical benefit could be demonstrated.

Conclusion

In routine clinical care, one third of GIST patients are systematically underexposed with a fixed dose of imatinib. Prospective clinical studies are needed to investigate the value of C_{min}-guided imatinib dosing in GIST patients.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal malignancies arising from the gastrointestinal tract. Activating mutations in *KIT* protooncogene receptor tyrosine kinase (*KIT*) or platelet-derived growth factor receptor (*PDGFR*), resulting in activation of the tyrosine kinase signalling pathway, are considered to be the main molecular drivers in GIST. Imatinib is a tyrosine kinase inhibitor (TKI), which targets protein kinases such as Bcr-Abl, KIT and PDGFRA and -B.(1) Since the introduction of imatinib, survival has improved spectacularly in advanced GIST patients, and recurrence-free survival has improved in the adjuvant setting. The recommended dose of imatinib is 400 mg, based on previous phase III studies.(2, 3) However, a large variability in plasma imatinib concentrations is observed during treatment.(4, 5) This variability may be caused by a range of factors. Imatinib is metabolized by cytochrome P450 (CYP) 3A4 and CYP3A5, and is also a substrate for drug transporters such as P-glycoprotein (P-gp; ATP-binding cassette sub-family B member 1 (ABCB1)) and breast cancer resistance protein (BCRP; ATP-binding cassette sub-family G member 2 (ABCG2)). Exposure may therefore be influenced by genetic polymorphisms and co-administered drugs.(6, 7) In addition, patients undergoing a major gastrectomy have been shown to have significantly lower C_{min} values than other patients (8), and one study has reported a significant decrease in exposure to imatinib over time.(9) Several trials have found a correlation between higher plasma imatinib concentrations and better response to treatment in GIST (4, 10–12) and chronic myeloid leukaemia (CML).(13–15) Given the increasing evidence that exposure is relevant to clinical outcomes and the large variability in pharmacokinetics, which may be even larger in routine clinical care than in clinical trials, measurement of plasma imatinib concentrations may be useful to guide treatment with this drug. Over the last 3 years, plasma samples have been drawn from GIST patients during routine outpatient visits at our institute. This study describes the pharmacokinetics and occurrence of underexposure to imatinib in a large observational cohort of GIST patients, with over 400 concentrations measured in more than 100 patients during routine outpatient care.

Methods

Patients

All GIST patients treated with imatinib at the outpatient clinic of the Netherlands Cancer Institute (NKI) were identified retrospectively and included in this study. Identification was done through a search in the database of the Dutch GIST Registry, containing all patients diagnosed with GIST from 2009 to 2014 and treated at five GIST centers in the Netherlands. Only patients treated at the NKI were included. Patients who were diagnosed before 2009 and had one or more plasma imatinib concentrations measured were identified separately, and their data were added manually.

Variables

Patient characteristics (sex and ethnicity) and tumor characteristics (location, size, mitotic index and mutation status) were extracted from the Dutch GIST Registry. The mutation analysis protocol included analysis of *KIT* (exons 9, 11, 13 and 17) and *PDGFRA* (exons 12, 14 and 18) by Sanger sequencing. Sequencing was performed on a capillary sequencer (ABI 3730 DNA Analyzer; Life Technologies, USA), and mutation analysis was performed using specific software (MutationSurveyer; Softgenetics, USA). Also, the treatment objective (palliative or (neo-)adjuvant), imatinib dose, dosing schedule and adverse events were included in the analysis. Past surgeries for GIST and surgery results were entered, as were concomitant medication and medical history. For patients diagnosed before 2009, patient files were used for extracting the aforementioned variables. Response evaluations were derived from regularly performed computed tomography (CT) scans and were performed according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. The best overall response was defined as the best response recorded from the start of imatinib treatment until disease progression/recurrence. Patients were classified as responders if their best response was found to be a complete response or a partial response. Patients were classified as non-responders if stable disease or progressive disease was their best response.

Pharmacokinetics

Blood samples were drawn during regularly scheduled visits at the outpatient clinic. The time of the last intake of imatinib and the time of the blood sampling were recorded. Plasma imatinib concentrations were determined using a validated liquid chromatography assay with tandem mass spectrometry.(16) An estimate of the imatinib C_{min} was calculated on the basis of the measured concentration and the interval between the last ingested dose and the sampling time, using the algorithm developed by Wang et al.(17) Adequate plasma imatinib concentrations were defined as imatinib C_{min} 1000 µg/L, as described in previous studies.(13, 15, 18) For the analysis, the first steady-state imatinib C_{min} was used. A representative C_{min} was defined as the first representative sample at least 2 weeks after the start of imatinib treatment.

Statistical analysis

Statistical analyses were executed using IBM SPSS Statistics 20 and R version 3.2.2. software.(19) Univariate and multivariate Cox regression, using relevant characteristics such as the *KIT* mutational status and the imatinib dose, were used for assessing the correlations of exposure to imatinib and time on imatinib treatment with the time to progression (TTP). Also, exploratory analyses using nonlinear mixed-effects modelling were conducted to evaluate changes in the imatinib C_{min} over time. Inter- and intrapatient variabilities were calculated using coefficients of variation. The association between imatinib C_{min} values and clinical and demographic variables—such as age, sex, tumor site,

surgery and tumor characteristics—was assessed using independent Mann–Whitney U tests. All tests were two sided, and a p value of <0.05 was considered significant.

Results

Between January 2009 and May 2014, 111 patients who received imatinib therapy were identified from the Dutch GIST Registry database. Not all patients had known imatinib C_{min} values. From August 2012 to December 2014, 582 plasma imatinib concentrations were measured in 123 GIST patients. An additional 33 patients who started imatinib treatment before 2009 and had imatinib drug concentrations measured were identified at the outpatient clinic. All samples below the lower limit of quantification were excluded, in case this was due to a planned end of treatment or interruption due to adverse events. Also, samples with a missing time of the last dose or of sampling and samples drawn within 2 weeks after the start of imatinib treatment were excluded. This resulted in 421 representative plasma imatinib concentrations from 108 patients included in the analysis. The median sample frequency per patient was 3 (range 1–11). Patient and tumor characteristics are described in Table 1. More than half of the cohort consisted of men (n = 60, 56.5 %), and the median age was 60 years (range 28–87) (Table 1). An overview of the distribution of the calculated imatinib C_{min} values in the patients studied in this cohort is given in Table 2. The median steady-state C_{min} was 1082 µg/L. Sixty patients (55.6 %) had adequate C_{min} values at steady state (Figure 1). Overall, 32.4 % of patients showed low imatinib C_{min} values in >75 % of their samples, and 33.3 % of patients showed adequate imatinib C_{min} values in all measured samples. Exposure to imatinib showed larger inter- and intrapatient variabilities, with relative standard deviations of 54 and 23 %, respectively.

Table 1: Patient characteristics.

Characteristic	Patients (*N* = 108)
Sex (male)	60 (55.6%)
Age [years; median (range)]	60 (28–87)
Tumor status	
Localized	59 (54.6%)
Metastasized	49 (45.4%)
Treatment objective	
Neo-adjuvant	16 (14.8%)
Adjuvant	30 (27.8%)
Palliative	62 (57.4%)
Location of primary tumor	
Stomach	46 (42.6%)
Small bowel	44 (40.7%)
Duodenum	2 (1.9%)
Rectum	7 (6.5%)
Oesophagus	2 (1.9%)
Colon	1 (0.9%)
Unknown	6 (5.5%)
Primary tumor size	100 (19–300)
Mutation status	
KIT exon 11	76 (70.4%)
KIT exon 9	9 (8.3%)
KIT exon 13	1 (0.9%)
KIT exon 17	3 (2.8%)
PDGFR exon 14	1 (0.9%)
PDGFR exon 18	5 (4.6%)
Wild type	3 (2.8%)
Unknown	10 (9.3%)

No significant change over time was found. The slope was estimated at a negligible 0.00004 day-1, with a relative standard error of 25 % ($p > 0.05$). The median time on imatinib was 27 months (range 1–161). Within the recorded follow-up period, 12 patients treated with palliative intent stopped imatinib because of progressive disease. No statistically significant difference in the TTP was found between patients with low steadystate C_{min} values (n = 27) and those with adequate C_{min} values (n = 35) in univariate Cox regression (hazard ratio 1.64, 95 % confidence interval 0.611–5.61; p = 0.43) (Figure 2). In multivariate analysis correcting for the imatinib dose, sex and KIT mutational status, the association between the C_{min} and TTP remained non-significant (hazard ratio 0.60, 95 % confidence

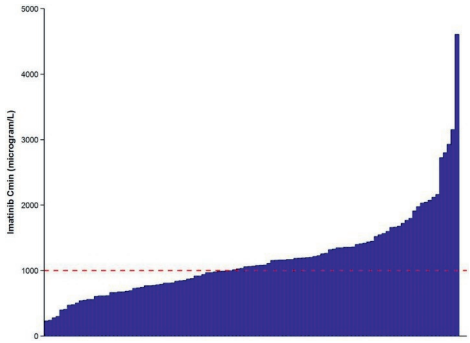

Figure 1:

Distribution of the 108 patients' first representative trough plasma imatinib concentration (C_{min}) values. The dotted red line indicates a C_{min} of 1000 µg/L.

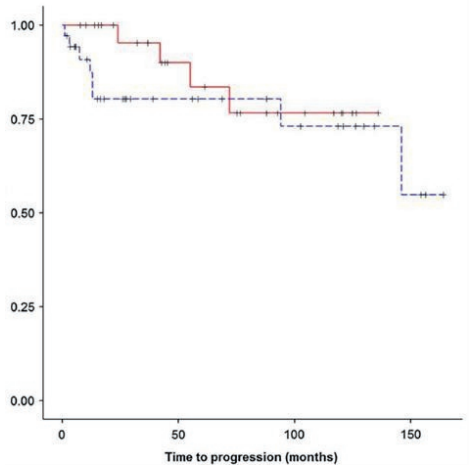

Figure 2:

Time to progression of gastrointestinal stromal tumor patients on imatinib treated with palliative intent as a function of the trough plasma imatinib concentration (C_{min}) at steady state. The dashed blue line indicates patients with an imatinib C_{min} C1000 µg/L (n = 35), and the solid red line indicates patients with an imatinib C_{min} <1000 µg/L (n = 27).

interval 0.53–6.35; p = 0.34). Of the 62 evaluable patients treated with palliative intent, 5 (8.1 %) were non-responders. The median C_{min} values were 1270 µg/L in patients showing a radiological response and 920 µg/L in non-responders (p = 0.23) (Figure 3). In the neo-adjuvant setting, no difference in imatinib C_{min} values was found between responders and non-responders, as all but two patients had a response. No clinical characteristic (age, type of surgery, sex, extent of resection) was predictive of low imatinib C_{min} values. Also, no association with tumor characteristics, such as the location (p = 0.54), tumor status at registry entry (p = 0.23) and mutation status (p = 0.48), was found. Four patients (3.7 %) discontinued imatinib treatment because of adverse events. No association with the imatinib C_{min} was found (p = 0.40).

Table 2: Characteristics of the 421 available plasma imatinib samples.

Characteristic	Patients, N = 108
C_{min} (µg/L); mean (range)[a]	1193 (227–4606)
C_{min} category	
<1000 µg/L	48 (44.4%)
≥1000 µg/L	60 (55.6%)
C_{min} <1000 µg/L in 75 % of samples	35 (32.4%)
C_{min} ≥1000 µg/L in all samples	36 (33.3%)
Received dose category	
<400 mg	8 (7.4%)
400 mg	86 (79.6%)
>400–800 mg	14 (13.0%)

C_{min}: trough plasma imatinib Concentration.
[a] Unless specified otherwise, the first representative C_{min} was used.

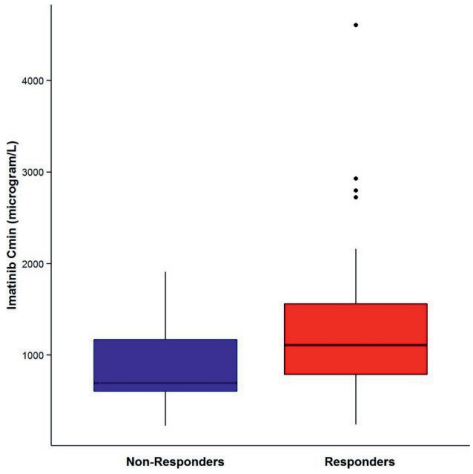

Figure 3:

Box plot of trough plasma imatinib concentration (C_{min}) values measured at steady state in non-responders (n = 5) and responders (n = 57) to palliative imatinib treatment. The median C_{min} values were 920 µg/L in non-responders and 1271 µg/L in responders.

Discussion

Several studies have linked higher imatinib C_{min} values to better treatment outcomes.(4, 10–13, 15) In CML, a threshold of ≥1000 µg/L has been recommended on the basis of several studies.(20–22) In GIST patients, a threshold of ≥1100 µg/L has been suggested.(20–22) This is based on a study by Demetri et al. (4), in which patients in the lowest C_{min} quartile (<1100 µg/L) had a shorter TTP and decreased clinical benefit. In our cohort, we found that a large proportion of patients were underexposed to imatinib even when a relatively low threshold of ≥1000 µg/L was used (Table 2; Figure 1). Although 92.6 % of patients received imatinib doses of 400 mg or higher,(40 % of our patients had imatinib C_{min} values <1000 µg/L in the first steady-state sample, and only one third of patients had adequate C_{min} values in every sample (Table 2). This suggests that GIST patients in routine clinical care have a higher risk of underexposure, which may even result in less clinical benefit.(4) The higher average C_{min} found by Demetri et al. (4) may have been due to a higher imatinib dose, as patients were randomized to receive either 400 or 600 mg once daily. But other studies in both CML and GIST patients have also described higher concentrations than those observed in our cohort.(11, 15) This could be explained by the fact that those previous studies were performed in a selected and regulated trial setting. In our cohort, no patient selection was made other than the diagnosis of GIST and treatment with imatinib. Although concomitant medication was strictly monitored to prevent possible interactions, no strict exclusion criteria for this study were set considering any concomitant medication causing an interaction for which no replacement was possible. Also, no exclusion criteria were set for comorbidities and laboratory results. Moreover, in routine clinical care, lack of patient compliance could be a factor. Besides the large percentage of underexposure in the first steady-state sample (relative standard deviation 54 %), we also found a large intrapatient variability of 23 %. Only one third of patients had adequate C_{min} values in every sample. This is in accordance with the findings reported by Yoo et al. (8), who also found large inter- and intrapatient variabilities of 44.7 and 26.5 %, respectively. An earlier prospective pharmacokinetic study found a significant decrease in systemic exposure to imatinib of almost 30 % within 90 days.(9) The authors hypothesized that this was a consequence of lower oral bioavailability with time, possibly due to upregulation of drug transporters or CYP3A4. Another explanation could be that the decrease in exposure to imatinib resulted from a decrease in alpha-1-acid glycoprotein (AGP) as a consequence of the impressive activity of imatinib treatment.(23) In our cohort, the large variability could not be explained by a change in C_{min} values over time. A later study also did not find a time-dependent decrease in exposure in a cohort of 65 patients, supporting our finding.(24) No clinical characteristic was found to be predictive of low imatinib C_{min} values. Although previous studies have reported lower imatinib C_{min} values after major gastrectomy, no correlation between C_{min} values and the extent of surgery was found in our study.(8) While previous studies have found a correlation between higher imatinib

C_{min} values and better clinical outcomes (4, 10–12), our results show that in routine clinical care, underexposure seems to be a substantial issue. Although no statistically significant relationships between exposure to imatinib and treatment response were found, we did find a trend towards responders having higher C_{min} values than non-responders in the palliative setting (Figure 3), and the same trend was found in neo-adjuvant patients. However, no correlation between the C_{min} and TTP was found in the palliative subgroup of patients (Figure 2). This lack of statistically significant differences could have been caused by the small number of non-responders and the limited number of progression events. Our study gives a new and representative insight into underexposure to imatinib in GIST patients in routine clinical care. We have shown that underexposure is a substantial problem in routine clinical care and that there are large inter- and intrapatient variabilities. Given the fact that several studies have described a correlation between C_{min} values and response, pharmacokinetically guided dose individualization—also known as therapeutic drug monitoring (TDM)—should be considered. One study attempted to demonstrate the benefits of TDM of imatinib but failed to do so because of small patient numbers and limited physician adherence to TDM recommendations.(25) A prospective clinical trial to assess the benefit of C_{min} guided imatinib dose adjustments in GIST patients is needed. Ideally, such a trial should use a relevant clinical endpoint, such as progression-free survival, because previous studies have found clear correlations between exposure to imatinib and efficacy, and we have now shown that underexposure is a frequent problem in routine clinical care of imatinib-treated GIST patients.

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Conflict of interest

Sheima Farag, Remy Verheijen, Martijn Kerst, Annemiek Cats and Alwin Huitema have no conflicts of interest that are directly relevant to the content of this study. As the principal investigator of the study, Neeltje Steeghs received a research grant from Pfizer, Novartis and Bayer for the Dutch GIST Registry.

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6

Chapter 6

Discussion and future perspectives

Gastrointestinal stromal tumor (GIST) is a rare mesenchymal malignancy in the gastrointestinal tract. Since the introduction of imatinib in 2002, a tyrosine kinase inhibitor (TKI) that targets Bcr-Abl, KIT and PDGFR, treatment of patients with advanced GIST has been spectacularly improved. The focus of this thesis is on treatment strategies and follow-up in GIST patients in general and in special subgroups.

Subgroups

In chapter 2 we discussed treatment strategies and treatment outcome in various subgroups of GIST patients. The first subgroup, discussed in paragraph 2.1, was the group of elderly patients, 75 years of age and older. The second subgroup, discussed in paragraph 2.2, was the group of *PDGFRA* exon 18 mutated GIST patients. And the last paragraph on subgroups, paragraph 2.3, described the characteristics of GIST patients with a germline KIT mutation. In all three subgroups we studied the outcome of imatinib treatment. We concluded that imatinib treatment is feasible and safe, even in elderly patients of 75 years and older. And we concluded that imatinib is an effective treatment option in most GIST subgroups, even in some primary resistant D842V-mutated GISTs. In the first paragraph of chapter 2, we described that in daily practice elderly patients receive less imatinib treatment, irrespective of performance score or comorbidity. We also found that in case of an adverse event imatinib was more often permanently discontinued in elderly patients with metastatic disease. Combining clinical data of all GIST patients in the country and aggregate this in a large nationwide dataset created the possibility of studying this rare subgroup of patients. For treating physicians the results of this study created a high level of awareness that we are most likely undertreating our elderly patients in current clinical practice.

Our results emphasize the importance of studies conducted in a geriatric population, especially since GIST is typically a disease of the elderly. Not only should we consider comorbidity and performance score in the treatment of these patients, we also need to personalize treatment outcome. For instance, since elderly patients in general have shorter expected overall survival, treatment outcome can also be quality of life rather than survival. In the Dutch GIST Registry database, we assess quality of life in the prospectively identified GIST patients. In the future, these quality of life questionnaires can be used to assess important patient reported outcome measures in the prospectively identified population. Quality of life data can also be used as an important parameter in the decision making to start adjuvant treatment in elderly GIST patients.(1) Especially, since the latest long-term study on adjuvant treatment showed that there is no difference in survival benefit between patients receiving adjuvant imatinib for 2 years and the control group. This can be especially useful in the elderly GIST population, where expected overall survival in general seems shorter and quality of life might be a better outcome than recurrence

free survival. In this case, one might wait until recurrence or disease progression and then introduce imatinib.

In paragraph 2.2 we advocate that, given the lack of alternative treatments in advanced disease, it may be worthwhile to start imatinib treatment in D842V-mutated GISTs with frequent response evaluations. In despite of this, we also found that over half of the patients with a D842V mutation in exon 18 of the *PDGFRA* gene had no treatment benefit and had progressive disease as best response. This resistance to imatinib is thought to be the result of D842V mutation affecting the tyrosine kinase receptor activation loop. A D842V mutation in *PDGFRA* leads to reduced accessibility of the adenosine triphosphate (ATP) pocket and thereby to relative resistance to imatinib.(2) At the moment, there are some promising smart molecular compounds like BLU-285 in clinical development.(3) BLU-285 is a drug that selectively targets activation loop mutations targeting KIT exon 17 and *PDGFRA* D842V mutations. In a phase 1 study it has shown partial response in 7 out of 17 D842V mutated GIST patients, while 10 out of 17 patients had stable disease. Moreover, due to its selective properties, BLU-285 was very well tolerated and no dose limiting toxicities occurred.(3) Another promising smart molecule compound is DCC-2618. This is a pan-KIT and *PDGFRA* switch control inhibitor. It has activity at both mutations occurring at the ATP binding pocket and the activation loop. However, a phase 1 trial with 57 GIST patients only 3 patients had a D842V mutation. Two out of them had ongoing responses at 44 and 30 weeks, although no partial response was noted.(4)

Besides the D84V mutated GISTs, we examined also non-D842V mutated GIST patients. Similar to prior research we found that *PDGFRA* exon 18 mutated GIST patients who have other mutations than the characteristic D842V mutation respond well to imatinib. (5) Therefore, we emphasize that detailed mutational analyses of the tumor is important prior to initiation of drug therapy.

In GIST patients harboring a germline KIT mutation, discussed in paragraph 2.3, we advocate that imatinib has a positive and long term efficacy and should therefore be considered in a life-long adjuvant/prevention setting in these patients. However, at the moment, data on prolonged imatinib treatment is scarce (imatinib registration in 2002) and we don't know what the long-term effects will be. This information is of significant importance especially in the younger patients described in both our cases and in previous literature. In the guideline Bachet et al provided, they stated that life-long adjuvant imatinib treatment should be considered in patients older than 35 years of age.(6) In our 23-year-old patient described in case 2 we started adjuvant imatinib. This was based on the multiple malignant GISTs. Whether or not she should continue imatinib after the regular adjuvant period of 3 years is debatable. In her case hyperplasia of the Cells of Cajal was found on the non-tumorous parts of her gastrointestinal tract and with the known KIT germline mutation and family history of multiple GISTs (mother) we considered that she is prone for more GISTs to arise and that the clinical implications, potential of incurable disease if metastases develop, will cause more harm than the well tolerated imatinib will.

Any treatment modality, whether it is surgical or systemic treatment, should however be discussed in multidisciplinary meeting for each individual harboring a germline KIT mutation independently.

The guideline by Bachet et al also described when to actively screen for a germline *KIT* mutation at presentation.(6) They report that around 5% of GIST cases with a tumor *KIT* or *PDGFRA* mutation harbor an underlying germline mutation. Data on this rare syndrome is however anecdotal and based on case reports. Active screening for patients with suspected germline KIT or *PDGFRA* mutation should therefore only be considered in case of a striking directive derived from age of diagnosis, medical history or symptoms.

In general, young age at diagnosis or multiple GISTs are more likely to be linked to syndromes associated with GISTs. GISTs in patients with hereditary syndromes are mostly wild type for *KIT* and *PDGFRA*. By far most pediatric GISTs are wild type for *KIT* and *PDGFRA*. (2) These GISTs are a heterogeneous group and each subtype within this group (SDHX deficiency, NF1 mutated, BRAF mutated, RAS mutated) has different characterization. (7) Also, responses to treatment and treatment outcome strongly differ between the subtypes. Therefore, future studies on GIST subtypes should also focus on GISTs wild type for *KIT* and *PDGFRA*.

Hematological toxicity

Although imatinib is currently the most effective treatment and side effects are mostly mild and clinically manageable, some adverse events are potentially dangerous and do reduce quality of life. In chapter 3 we describe the occurrence of hematologic toxicities. For now it remains unclear which patients are at risk for developing hematologic toxicity. A low ANC and low hemoglobin concentration at the initiation of imatinib are potential risk factors.(8,9) In paragraph 3.1 we describe the occurrence and management of imatinib induced agranulocytosis. In our cases, neutropenia occurred within approximately one month after initiation of imatinib. All our patients experienced full recovery of the neutrophil count only a few days after discontinuation. Also, reintroduction of imatinib was safe in our cases. Therefore, in our opinion imatinib treatment should not be withheld in patients after a first episode of agranulocytosis.

The most common hematological toxicity, however, is anemia. Over 90% of patients receiving imatinib have anemia.(8) Anemia causes fatigue, which does impair quality of life and is therefore an important issue in GIST patient treated with imatinib. Its etiology in the treatment of GIST is unclear and to date no clear risk factors for developing clinically relevant anemia are identified. In the Dutch GIST registry each visit is entered and registration of hematologic and chemical laboratory values is performed longitudinally. Capturing all these data points in a pharmacodynamics model might help to better understand this multifactorial problem and can potentially identify the most important risk factors for developing clinically relevant anemia.

Response evaluation

Currently, standard response evaluations in GIST are performed using CT-scan and responses are mostly expressed as a decrease or increase of size. However, prior research has shown that besides a decrease in size, a decrease in tumor density correlates with better outcome. One of the limitations of a CT scan is that volume response takes up to 6 to 9 months before it can be measured and a decrease in density is not always seen. FDG-PET could measure responses within 1 to 8 days.(10) International guidelines recommend early response assessment by FDG-PET in patients treated with neo-adjuvant intent to prevent delay of surgery.(11) However, up till now it was unclear whether FDG-PET did indeed change management in in daily practice. In Chapter 4 we show that, in a nationwide series of imatinib treated GIST patients, in most patients FDG-PET scans made for early response evaluation in the neo-adjuvant setting do not result in a change in management. Only for the subgroup of patients with GIST harboring a non- *KIT* exon 11 mutation, FDG-PET scans resulted in a change in management (in half of the cases). We therefore advise to consider FDG-PET evaluation in this curative neo-adjuvant setting (with exclusion of patients with a GIST harboring the high imatinib sensitive *KIT* exon 11 mutation).

Also, in palliative setting response evaluation using FDG-PET might optimize individual treatment.(12) FDG-PET is thought to be helpful in identifying single active lesions in metastatic disease and can help decision making whether a metastasectomy should be performed rather than moving on to the next line of systemic treatment. However, to date the role for FDG-PET in international guidelines is limited. Also no prior research has been performed to study the usefulness of FDG-PET in the decision making process in metastatic GIST patients. In Paragraph 4.2 we show that, in contrast to neo-adjuvant treated GIST patients, patients treated in palliative setting do not benefit from early response evaluation using this imaging technique. FDG-PET does, however, seem to change management in case of late response evaluation. These analyses are performed in a preselected group of patients, suggesting that this might primarily be beneficial in case of a predefined indication. Because of the limited number of metastasectomies in our database, it was not possible to assess the usefulness of FDG-PET for this specific indication. In the future, a multinational collaboration using multiple databases should be performed to assess this specific matter.

A limitation of FDG-PET is that a small portion of tumors does not show any FDG-avidity and therefore it is not always possible to evaluate response using FDG-PET. To date it is unclear what the mechanisms underlying this variability in FDG avidity and what characterizes these FDG-PET negative GISTs. In the future, using other radiopharmaceuticals might create a better and more sensitive method for response evaluations in GIST. This might lead to more optimized individual treatment decisions.

Pharmacokinetics

To optimize treatment efficacy of all oral tyrosine kinase inhibitors used in GIST patients (imatinib, sunitinib and regorafenib) therapeutic drug monitoring is advocated. Therapeutic drug monitoring is giving the for that individual patients' optimal dose of the drug based on the drug levels that are measured in the blood of the patient. Several trials have found a correlation between higher imatinib plasma concentrations and better response to treatment in GIST and CML.(13,14) Given the increasing evidence that exposure is relevant to clinical outcome and the large variability in pharmacokinetics, which may be even larger in routine care than in clinical trials, measuring imatinib plasma concentrations may be useful to guide treatment of this drug. In Chapter 5 we found that a large proportion of patients was underexposed to imatinib. A prospective clinical trial to assess the effect of individually dosed imatinib based on measured C_{min} is needed, ideally with a relevant clinical endpoint such as PFS, as previous studies have found clear correlations between imatinib exposure and efficacy and we now show that underexposure is a serious problem in routine clinical care.

Resistance to imatinib treatment is a big problem in palliative setting Currently, a phase II/III study on alternating imatinib with regorafenib in the first line of treatment assesses whether alternating between drugs might delay the development of drug resistance mutation. However, similar to sunitinib, regorafenib has even more and higher grade adverse events and have proven to improve progression-free survival with merely a couple of months.(2) Also, overall survival does not seem to improve. Moreover, every tyrosine kinase inhibitor seems to have its own resistance pattern. New smart molecule compounds are currently being developed and assessed, like the priorly mentioned DCC-2618, that show promising results and seem to overcome this resistance problem with a milder toxicity profile than the currently approved tyrosine kinase inhibitors used in second and third line metastatic setting. I believe that in the future not only individualizing dosing, alternating tyrosine kinase inhibitors and also the sequence of second, third and even fourth line treatment is going to change and will improve the life expectancy and quality of life of GIST patients.

In conclusion, GIST is a rare disease and although treatment has spectacularly improved, for many subgroups more research is still needed. Considering the rarity of this tumor multicenter studies are necessary to acquire data on a sufficient number of patients. The Dutch GIST registry is a good example of a successful multicenter collaboration, resulting in increased research on GIST leading to an improvement in life expectancy and quality of life of current and future GIST patients.

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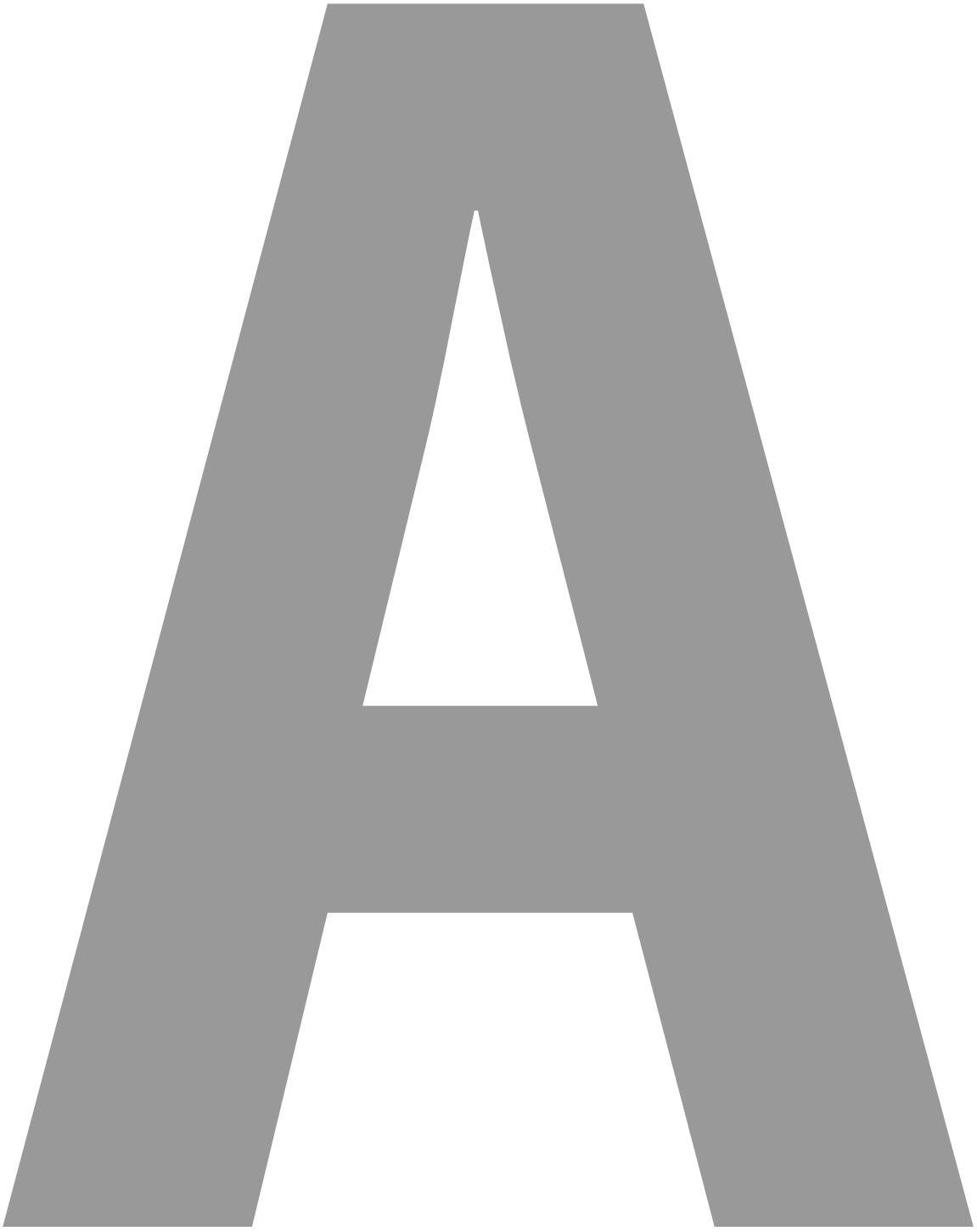

Appendices

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Summary

Gastrointestinal stromal tumor (GIST) is a rare mesenchymal malignancy in the gastrointestinal tract. Since the introduction of imatinib in 2002, a tyrosine kinase inhibitor (TKI) that targets Bcr-Abl, KIT and PDGFR, treatment of patients with advanced GIST has been spectacularly improved. In this rapidly evolving field, more insight is needed the treatment and follow-up of GIST patients. The focus for this thesis is on treatment strategies and follow-up in GIST patients in daily clinical practice using a large comprehensive multicenter database.

In Chapter 2 different subtypes of GIST are discussed. One of the highest incidences of GIST is found in the age group of patients 75 years of age and older. In paragraph 2.1 we found that irrespective of performance status or comorbidity, elderly GIST patients (75 years and older) with localized disease received less treatment. Surgery was significantly less performed and in case of resection of a high-risk tumor, adjuvant treatment was given significantly less in elderly patients. Meanwhile, both primary resection and adjuvant imatinib treatment seem feasible and effective treatments in elderly GIST patients with localized disease. An objective evaluation of comorbidity using the CCI might improve the decisions-making process in elderly GIST patients.

In paragraph 2.2 we studied the most common *PDGFRA* mutation, a D842V substitution in exon 18, shows primary resistance to imatinib in in vitro and in vivo studies. Although D842V-mutated GISTs comprise a large majority of *PDGFRA* exon 18 GISTs, other mutations in exon 18 differ in their sensitivity to imatinib. It is therefore important to distinguish between resistant and sensitive mutations. Interestingly, we showed that a small fraction of D842V-mutated GISTs respond to treatment with imatinib. Therefore, in our view imatinib treatment should not be universally denied in D842V-mutated GISTs who are not surgically resectable.

The last paragraph on subgroups, paragraph 2.3, describes the effects of imatinib on the GISTs and the cutaneous hyperpigmentation associated with a germline *KIT* mutation (p.Trp557Arg) in two related GIST patients. Additionally, we give an overview of literature on the effect of imatinib in GIST patients harboring a germline *KIT* mutation. We show a remarkable and long term effect of imatinib in the GISTs and a striking effect on the pigmentation anomalies of the skin. Imatinib treatment should therefore be considered in these patients.

In Chapter 3 we studied hematological toxicities, since it remains unclear which patients are at risk for developing hematologic toxicity. A low ANC and low hemoglobin concentration at the initiation of imatinib are potential risk factors. In paragraph 3.1 we describe the occurrence and management of imatinib induced agranulocytosis. In our cases, neutropenia occurred within approximately one month after initiation of imatinib. In case of clear agranulocytosis, cessation of imatinib treatment remains crucial to avoid further hazardous exposure. All our patients experienced full recovery of the neutrophil

count only a few days after discontinuation of imatinib. Reintroduction of imatinib was in all our cases successful. We therefore recommend a re-challenge with imatinib is usually effective in locally advanced and metastatic GIST and a re-challenge with imatinib after a first episode of agranulocytosis and full recovery of the neutrophil count.

International guidelines recommend early response assessment by FDG-PET in patients treated with neo-adjuvant intent to prevent delay of surgery. However, to date no prior study has assessed the actual influence of FDG-PET on treatment strategies. In Paragraph 4.1 a nationwide series of imatinib treated GIST patients harboring non- *KIT* exon 11 mutations FDG-PET scans made for early response evaluation in the neo-adjuvant setting results in a change in management in half of the cases. We therefore advise to consider FDG- PET evaluation in this curative setting. Paragraph 4.2 on the other hand shows no benefit of early response evaluation using FDG-PET in patients treated in palliative setting. In case of a predefined indication over half of the late response FDG-PETs has led to change in management.

Several trials have found a correlation between higher imatinib plasma concentrations and better response to treatment in GIST and CML. In Chapter 5 we found that a large proportion of patients was underexposed to imatinib. This suggests that patients in routine care have a higher risk for underexposure, which may even result in less clinical benefit.

In conclusion, GIST is a rare disease and although treatment has spectacularly improved, for many subgroups more research is still needed. Considering the rarity of this tumor multicenter studies are necessary to acquire data on a sufficient number of patients. The Dutch GIST registry is a good example of a successful multicenter collaboration, resulting in increased research on GIST leading to an improvement in life expectancy and quality of life of current and future GIST patients.

Samenvatting

Gastrointestinale stromaceltumor (GIST) is een zeldzame mesenchymale tumor die voorkomt in het gastrointestinale stelsel. Sinds de introductie van imatinib in 2002, een tyrosine kinase remmer (TKI) die bindt aan Bcr-Abl, KIT en PDGFR receptoren, is de behandeling van gevorderde GIST spectaculair verbeterd. In het licht van deze snelle evolutie in het veld, is meer inzicht nodig in de huidige behandelstrategieën en follow-up van de patiënten met GIST. Dit proefschrift focust zich op behandelstrategieën en follow-up van GIST patiënten in de dagelijkse klinische praktijk, gebruikmakend van een grote en uitgebreide multicenter database.

In Hoofdstuk 2 wordt de behandeling van verschillende subtypen van GIST tegen het licht gehouden. De een na hoogste incidentie van GIST bevindt zich in de leeftijdscategorie van patiënten van 75 jaar en ouder. In paragraaf 2.1 hebben we gevonden dat los van performance status en comorbiditeit, juist deze groep patiënten minder vaak geopereerd worden en minder vaak adjuvant behandeld worden. Tegelijkertijd hebben we aanwijzingen gevonden waaruit blijkt dat zowel chirurgie als systemische therapie in deze groep een veilige en effectieve behandeling zijn. Een objectievere evaluatie van comorbiditeit, bijvoorbeeld gebruikmakend van de CCI, zou beslissingen rondom de behandeling van oudere patiënten met GIST kunnen verbeteren.

In paragraaf 2.2 hebben we de meest voorkomende *PDGFRA* mutatie, de D842V substitutie in exon 18, bestudeerd. Eerdere in vivo en in vitro studies hebben laten zien dat GISTen deze mutatie primair resistent zijn voor imatinib behandeling. Anderzijds, andere *PDGFRA* exon 18 gemuteerde patiënten lijken wel goed te reageren op imatinib. Het is daarom van belang om in een vroeg stadium aan tonen van welke soort *PDGFRA* exon 18 mutatie er sprake is. In onze populatie laten we desondanks zien dat een klein deel van de *PDGFRA* exon 18 gemuteerde GISTen met een D842V mutatie wel degelijk respons laten zien. Daarom zou in onze optiek imatinib behandeling, ook in deze groep, niet bij voorbaat al uitgesloten moeten zijn. Op dit moment zijn er namelijk geen andere alternatieven in de behandeling van GIST patiënten met deze mutatie in een vergevorderd stadium. Derhalve zou imatinib behandeling in deze groep gestart kunnen worden, waarbij er frequente respons evaluaties plaats zouden moeten vinden.

In de laatste paragraaf van dit hoofdstuk, paragraaf 2.3, worden de effecten imatinib beschreven in een familie met kiemcel *KIT* mutatie. Niet alleen op de GIST, maar ook op de hyperpigmentatie, bleek imatinib een langdurig positief effect te hebben. Imatinib zou daarom in deze groep patienten te allen tijde overwogen moeten worden.

In Hoofdstuk 3 hebben we imatinib geïnduceerde hematologische toxiciteit bestudeerd. Tot op heden is het onduidelijk welke patiënten risico lopen op zo een toxiciteit. Een laag granulocyten getal en laag hemoglobine concentratie voor de start van imatinib behandeling potentiele risico factoren. In paragraaf 3.1 beschrijven we het voorkomen en de behandeling van imatinib geïnduceerde agranulocytose. In onze casus ontstond

de neutropenie ongeveer een maand na start van de behandeling van imatinib. In dat geval is staken van de imatinib behandeling van levensbelang om erger te voorkomen. In alle beschreven patiënten was er binnen een aantal dagen na staken van imatinib al sprake van herstel van het granulocyten getal. Bovendien was herintroductie van imatinib in alle gevallen succesvol. Daarom raden wij aan dat herintroductie van imatinib niet alleen effectief is voor behandeling van gevorderde GIST, maar ook veilig is na volledige verbetering van de granulocyten getal.

In internationale richtlijnen wordt vroege respons evaluatie middels FDG-PET geadviseerd in patiënten die behandeld worden in neo-adjuvante opzet. Het idee is om zo een mogelijke vertraging van chirurgie te voorkomen. Er is echter tot op heden geen eerdere studie gedaan naar de invloed van FDG-PET op behandelstrategieën in GIST patiënten. In paragraaf 4.1 laten we zien dat in de helft van de neo-adjuvant behandelde patiënten met een mutatie anders dan *KIT* exon 11 FDG-PET invloed heeft gehad op de behandeling. Daarom adviseren wij in deze curatief in opzet behandelde groep patiënten vroege respons evaluatie middels FDG-PET. Aan de andere kant beschrijven we in paragraaf 4.2 juist dat in patiënten behandeld palliatief in opzet een vroege respons evaluatie juist niet zinvol is. Voornamelijk later in de behandeling leidt in geval van een specifieke indicatie het verrichten van een PET scan in meer dan de helft van de gevallen tot verandering van beleid.

Verschillende studies hebben een correlatie gevonden tussen hogere imatinib plasma spiegels en een verbetering in respons op de behandeling van GIST en CML. In hoofdstuk 5 hebben we echter gevonden dat een groot deel van de onderzochte patiënten een lagere expositie van imatinib hadden. Dit suggereert dat in de huidige praktijk patiënten een groter risico lopen op onderbehandeling, waarbij er zelfs sprake zou kunnen zijn op een slechter behandelresultaat.

Concluderend, GIST is een zeldzame ziekte en hoewel de behandeling spectaculair is verbeterd, is in veel subgroepen meer onderzoek nodig. Gezien de zeldzaamheid van deze tumor, is een multicenter samenwerking onmisbaar voor het verkrijgen van representatieve data in een voldoende aantal patiënten. De Nederlandse GIST registratie is een goed voorbeeld van een succesvolle multicenter samenwerking die heeft geresulteerd in een groter aantal onderzoeken naar GIST die leiden tot verbetering van levensverwachting en kwaliteit van leven in de huidige en toekomstige patiënten met GIST.

Dankwoord

Uiteraard zou dit proefschrift nooit tot stand zijn gekomen zonder de nodige hulp en ondersteuning van een fantastisch team aan promotores, begeleiders, co-auteurs, collega's en de allerliefste vrienden en familie.

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Curriculum Vitae

Sheima Farag was born on the 8th of November 1987 in Heemstede, The Netherlands. In 2006 she completed her secondary education at Athenaeum College Hageveld in Heemstede. In the same year she began her medical studies at the University of Amsterdam, during which she completed several clinical and research internships in Amsterdam and abroad. Her interest in oncology was triggered during her third year of college, in 2009, when she did a clinical internship on the Department of Medical Oncology & Hematology of the American University Hospital of Beirut (Lebanon). This experience led to the choice for a research internship at the Department of Thoracic Oncology of the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, where she conducted a study on thoracentesis in patients with malignant pleural effusion. In 2010 she went to the National Cancer Institute in Cairo (Egypt) for a clinical internship at the Department of Medical Oncology. After this experience she did a research internship in the lab of Prof. dr. Sjaak Neefjes where she helped in determining the efficacy of multiple drug compounds on lung cancer and head and neck cancer. Sheima graduated in 2013 and then started as a medical oncology resident in the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital. In 2014 she started her PhD research under supervision of her co-promotor dr. Neeltje Steeghs (Department of Medical Oncology) and promotor Prof. Dr. Hans Gelderblom (Department of Medical Oncology, Leiden University Medical Center), the results of which are presented in this thesis. After her PhD she has worked as Senior House Officer at the Medical Center Slotervaart until it unfortunately was closed by the end of 2018 as a result of bankruptcy. In February 2019 she moved together with her husband and two daughters to London were she has worked as a Clinical Research Fellow in the Sarcoma unit at the Royal Marsden Hospital. Since April 2020 she has been working as a Clinical Fellow for the Lung and Renal/Melanoma units at the same center.

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