

Side-effects from imatinib treatment of advanced GIST-associated with a better outcome

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Abstract

Background: Imatinib is considered to be the first-line therapy for patients with unresectable and/or metastatic gastrointestinal stromal cell tumors (GIST). The aim of this study was to analyze the occurrence of side-effects and clinical outcome.

Materials & Methods: 75 consecutive patients (41♂; median age 62 years, range 34-82), with GIST, who had received pre- and/or postoperative imatinib, were retrospectively reviewed. Chi-square test was used to compare the occurrence and distribution of side-effects and the Kaplan-Meier method was applied for survival analysis.

Results: The median follow-up time from the initiation of imatinib treatment was 48 months (4-107); median size of tumor was 10.3 cm (2.5-28) cm. Moderate to severe or life-threatening toxic reactions from imatinib treatment were registered in 30/75 patients (17/34♀). Most of the side-effects occurred early, 18/30 within the first month of imatinib treatment. Life-threatening complications occurred in two cases: agranulocytosis and tumor perforation. For the group of patients with metastatic or recurrent GIST (n=34), presence of side-effects and female gender were associated with increased recurrence-free survival (P =0.01).

Conclusions: Our findings indicate that side-effects from imatinib treatment are common. Their occurrence may be associated with a better outcome for patients with GIST.

Keywords: GIST, imatinib, side-effects, outcome

Introduction

Gastrointestinal stromal cell tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. The prevalence is 7-15/100 000, and about 50% are localized at the time of diagnosis [1,2]. GISTs are resistant to conventional chemotherapy and radiation and the risk of localized peritoneal or metastatic relapse after tumor resection is high [3-6]. All GISTs should be considered as potentially malignant; the standard treatment is complete tumor resection with negative tumor margins [7]. However, in many cases surgery alone is not curative. One in two patients with GIST will relapse after complete tumor resection, underlining the need for adjuvant medical treatment [5].

Mutations of the *KIT* proto-oncogene are central in the pathogenesis of GIST and the tumors are most often characterized by strong immunoreactivity to the KIT protein, the CD117 antigen [8-10]. The introduction of inhibitors of KIT tyrosine kinase has resulted in significantly improved outcomes of patient with advanced GIST. Imatinib mesylate is the tyrosine kinase blocker approved as the first-line treatment for patients with unresectable and/or metastatic GIST and for adjuvant treatment of patients with a significant risk of relapse [11-13]. Neoadjuvant (also called downstaging) treatment with imatinib may permit organ preservation and admit the possibility of radical margins of nonresectable GIST [14,15]. Adjuvant treatment offers improve-

ment in progression-free survival [13]. In addition, subsets of patients are treated with imatinib in a palliative or recurrent disease setting. Since the outcome seems to be improved by an extended treatment period, patients with a high risk of GIST relapse will be treated with imatinib for many years.

Although the medication is generally well tolerated, virtually all patients will have at least one adverse event [16]. Doubling the dosage of imatinib from the standard level (400 mg daily) to a high dose (400 mg twice daily) increases the incidence of severe adverse events [13,17]. However, no correlation could be seen between imatinib plasma trough level and previous grade 3 to 4 toxicity in patients taken a standard dose of 400 mg daily, but there was a significant correlation to plasma albumin and creatinine clearance [18]. Low plasma concentrations of imatinib have been associated with a shortened time to disease progression [19]. Determination of the plasma concentration of imatinib is still not used routinely in clinical practice and the only practical guideline for interpreting the concentration is the recommendation to keep it above 1,100 ng/mL. Adverse effects may reduce the patient's adherence to treatment; discontinuation of imatinib treatment has been reported to result in rapid tumor progression in patients with advanced GIST [20].

The aim of this study was to evaluate the occurrence and the prognostic significance of side-effects from imatinib treatment. For this purpose a single-center cohort of GIST patients was retrospectively reviewed concerning tumor characteristics, treatment and side effects, in relation to disease recurrence and survival during follow-up.

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Materials and Methods

Cases

The records of 75 consecutive GIST patients who received imatinib treatment at the Karolinska University Hospital, Sweden were retrospectively reviewed. All patients had been subjected to surgery and the initiation of imatinib treatment between February 2002 and July 2010. The study was approved by the ethical committee at the Karolinska University Hospital, Stockholm, Sweden.

The clinical data are summarized in Table 1. The radicality of the surgical resection and margins was classified as radical surgery with tumorfree resection margin (R0); intralesional surgery with microscopic infiltration of the resection margin (R1) or tumor reduction with gross residual disease (R2). The GIST diagnosis was established according to consensus criteria [9]. Immunohistochemical analysis of CD117 was performed in routine histopathology for all cases. Data from mutational analyses of the *KIT* gene exon 9, 11, 13 and 17, and the *PDGFRA* gene exon 12 and 18 in routine histopathology were retrieved where available. The risk of recurrence was defined using the modified classification of Fletcher-Miettinen, based on primary tumor size, location and mitotic index [21] (Joensuu, 2008). Tumor size was estimated on the radiological view if the imatinib treatment was initiated preoperatively, and on the histopathological measurement for cases only treated postoperatively. The observed tumor sizes ranged from 2.5 cm to 28 cm and were subgrouped as <5 cm, 5-10 cm, or >10 cm (Table 1). The primary tumor locations were esophagus (n=2), stomach (34), duodenum (7), small intestine (24), colorectal (7) or uncertain (1). The mitotic index of tumors was defined as the number of mitoses per 50 high-power fields (HPF). Sixty-nine patients fulfilled the criteria of high risk, *i.e.* risk intestinal tumors with tumor size ≥ 5 cm or ≥ 5 mitoses/50 HPF and gastric tumors with tumor size ≥ 10 cm or ≥ 5 mitoses/50 HPF). The other six patients were classified as intermediate risk *i.e.* intestinal tumors with tumor size 2-5 cm or ≤ 5 mitoses/50 HPF and gastric tumors with tumor size 5-10 cm or ≤ 5 mitoses/50 HPF.

Metastatic spread was observed of peritoneal, hepatic, or pleural types. Metastatic or recurrent disease was diagnosed before initiation of imatinib therapy in 31 cases; another 3 cases were defined to have metastatic disease as a consequence of earlier invasive procedures (exploratory laparotomy with open biopsy or external drainage).

The imatinib treatment groups are presented in Figure 1. Imatinib treatment initiated preoperatively with the intention of later radical surgical removal of tumor including any metastatic disease was defined as neoadjuvant, and the corresponding treatment initiated postoperatively was defined as adjuvant. Treatment initiated after radically intended surgery for recurrent disease and palliative treatment were grouped separately. Forty-one patients without metastatic disease received neoadjuvant or adjuvant imatinib due to high or intermediate risk GIST. Another 34 patients with metastatic disease received imatinib in a neoadjuvant, palliative, recurrent disease or adjuvant setting. Twenty patients received neoadjuvant treatment for a median of 7 months (range 5 days-23 months) preoperatively. Plasma concentrations of albumin and creatinine prior to start of imatinib treatment have been used in the calculations and renal function (creatinine clearance) was estimated using Cockcroft-Gault's

formula: $(140 - \text{age}) * (\text{weight} / \text{creatinine}) * (1.23 \text{ in men or } 1.04 \text{ in women})$. Eight patients had no available recorded weight before initiation of imatinib treatment but all of them had creatinine within normal range (Table 1). The history of moderate to severe or life-threatening side-effects were classified according to Common Terminology Criteria for Adverse Events v4.0 (CTCAE) by which side effects are classified as grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life threatening) or grade 5 (death related to adverse effects). All patients were followed-up routinely for tumor recurrence by means of abdominal cross-sectional imaging (computed tomography, MRI or ^{18}F Fluorodeoxyglucose positron emission tomography). Tumor response was evaluated by FDG-PET (11 cases in the neoadjuvant group) and/or contrast-enhanced computed tomography (n=75) and histopathological examination of the excised tumor (n=75). Follow-up was defined as time from initiation of imatinib treatment to last documentation of state [no evidence of disease (NED), evidence of disease (ED) or death].

Statistics

Statistical analysis was performed with the PASW for Windows statistical package (18.0; PASW Inc., Chicago, IL). Recurrence-free survival was measured from the start of imatinib treatment to the time of first recurrence or most recent follow-up or death, tested with the log rank test and plotted by the Kaplan-Meier method. Pearson's Chi-square test was used to compare the distribution of patient and tumor characteristics between groups; $P < 0.05$ was considered to be statistically significant.

Results

Imatinib treatment and side effects

The median follow-up time from the initiation of imatinib treatment until the last examination or death was 48 months (4-107; Table 1). Moderate to severe or life-threatening toxic reactions from imatinib treatment were registered in 30/75 patients (17/34♀, Table 2, Supplemental Table A). There was no statistically significant difference in the prevalence of side-effects between patients with or without metastatic disease ($P=0.78$), or between different groups of treatment settings ($P=0.44$, Figure 1), neither did we find any differences in relation to gender distribution ($P=0.11$) or to age at the initiation of imatinib treatment ($P=0.45$) (Figure 1, Table 2). Life-threatening complications occurred in two cases treated for metastatic GIST (Table 2). In Case no 29 the imatinib treatment was discontinued following development of agranulocytosis and sepsis. Case no 19 developed tumor perforation and was operated acutely, without interruption of imatinib treatment. In the other 28 patients, the most common side-effects were dermatitis/rash (n=15), gastrointestinal (9), edema (7), and muscle cramps (4). Fatigue was observed twice, and in addition several other side effects were noted in single patients.

Most of the side-effects occurred early, 18/30 within the first month of imatinib treatment. In 9 cases (Case number 5-8, 10, 12, 14, 29 and 30, Table 2), the imatinib treatment was interrupted within 3 months because of one or more of the following side-effects: agranulocytosis with sepsis (n=1), dermatitis, rash (6), pruritus (2), edema (2), nausea, diarrhea (3), myalgia and muscle cramps (1).

Table 1. Summary of clinical characteristics for all patients.

Parameter (informative n=)	No metastatic disease n=41	Metastatic or recurrent disease n=34	All GIST cases n=75
Gender (n=75)			
Female / Male	17♀/24♂	17♀/17♂	34♀/41♂
Age at start of imatinib (n=75)			
Median years (min-max)	62 (34-82)	61 (38-82)	62 (34-82)
Patient weight (n=67)			
Median kg (min-max)	75 (45-97)	72 (56-95)	73 (45-97)
BMI (n=65)			
Median kg/m2 (min-max)	25.3 (17.0-34.8)	24.1 (19.1-30.8)	24.9 (17.0-34.8)
Albumin (n=74)			
Median g/l (min-max)			
side effects +	40 (30-44)	33 (23-47)	37 (23-47)
side effects -	38 (30-47)	38 (20-46)	38 (20-47)
Creatinine clearance (n=67)			
Median ml/min (min-max)			
side effects +	103 (49-134)	108 (60-148)	104 (49-148)
side effects -	120 (28-175)	90 (46-140)	100 (28-175)
Tumor location (n=75)			
Esophageal	1	1	2
Stomach	19	15	34
Duodenal	4	3	7
Small intestine	11	13	24
Rectal	6	1	7
Uncertain	0	1	1
Metastases (n=75)			
No metastasis	41	0	41
Hepatic	0	17	17
Extrahepatic	0	17	17
- intraabdominal	0	15	15
- pleural	0	2	2
Tumor size (n=75)			
<5 cm	6	3	9
5-10 cm	16	8	24
>10 cm	18	19	37
Missing data	1	4	5
Risk classification (n=75)			
Low	0	0	
Intermediate	6	0	
High	35	34	
c-kit expression (n=75)			
CD 117 positive	41 (100%)	34 (100%)	75 (100%)
Mutation status (n=39)			
KIT exon 11 mutation	15	11	26
KIT exon 9 mutation	0	1	1
PDGFRA mutation	1	0	1
Wild-type	5	6	11
Initial indication for imatinib (n=75)			
Neoadjuvant	10	10	20
Adjuvant	31	2	33
Recurrent	0	10	10
Palliative	0	12	12
Surgery / Margin (n=75)			
Radical / R0	27	15	42
Intralesional / R1	14	14	28
Tumor reduction / R2	0	5	5
Time of follow-up from initiation of imatinib treatment (n=75)			
Median months (min-max)	51 (8-107)	44 (4-105)	48 (4-107)
Follow-up (n=75)			
Alive, NED	36	14	50
Alive, Stable disease	1	5	6
Recurrence (reoperated)	7 (6)	15 (10)	22 (16)
† from GIST	4	12	16
† from other cause	0	3	3

BMI = Body mass index; NED = No evidence of disease at the end of follow-up; † = Dead

Table 2. Details of the 30 patients with moderate, severe or life-threatening side effects from imatinib treatment.

Case no	Treatment setting	Time to side effect (months)	Side effects if imatinib type	grade	Treatment (months)	Stop of imatinib	Follow-up (months)	Reurrence / reoperation	Follow-up outcome
No metastatic disease									
1	NeAd	<1	deafness, dizziness	2	4	yes	30	no	alive, NED
2	NeAd	<1	dermatitis, headache, muscle cramps	2	24	no	43	no	alive, NED
3	NeAd	<1	nausea, vomiting, anorexia	2	11	no	20	no	alive, NED
4	Ad	<2	dermatitis, rash	2	4	yes	60	yes / no	† (GIST)
5	Ad	<1	dermatitis, rash, hepatopathia	2	2	yes	100	no	alive, NED
6	Ad	<2	dermatitis, rash, pruritus, edema	2	3	no	105	no	alive, NED
7	Ad	<1	dermatitis, rash, pruritus, gastro-intest bleeding	2	2	yes	79	no	alive, NED
8	Ad	<1	diarrhea	2	<1	yes	47	no	alive, NED
9	Ad	<1	myalgia, muscle cramps, nausea	2	37	no	41	no	alive, NED
10	Ad	<1	muscle cramps, nausea	2	<1	yes	85	no	alive, NED
11	Ad	4	fatigue, dermatitis, rash	2	5	yes	64	no	alive, NED
12	Ad	<1	dermatitis, rash	2	3	yes	51	no	alive, NED
13	Ad	<1	edema, dermatitis, rash	2	22	no	58	no	alive, NED
14	Ad	<1	dermatitis, rash	2	<1	yes	18	no	alive, NED
15	Ad	<1	dermatitis, rash	2	12	yes	20	no	alive, NED
16	Ad	>6	edema (angio- tung)	3	11	yes	38	no	alive, NED
17	Ad	<1	diarrhea, anorexia	2	80	no	100	yes / yes	ED
Metastatic / Recurrent disease									
18	NeAd	<1	nausea, anorexia, edema	2	97	no	101	no	alive, NED
19	NeAd	<1	tumor perforation, acute surgery	4	18	no	18	no	alive, NED
20	NeAd	<2	dermatitis, rash	2	4	yes	63	yes / yes	ED
21	NeAd	18	nausea, anorexia	2	40	no ^{□□}	43	no	alive, NED
22	NeAd	8	neuropathia, edema, fatigue	2	67	yes	88	yes / yes	ED
23	NeAd	<3	dermatitis, rash	2	7	yes	21	no	† (mesothelioma)
24	Pal	27	hypothyroidism	2	29	no	36	PD	†(GIST)
25	Pal	<1	dermatitis, rash	2	21	no	27	yes / yes	alive, NED
26	Rec	<3	muscle cramps, nausea	2	84	no	105	no	alive, NED
27	Rec	30	polyneuropathia, progressive	2	36	yes	59	no	alive, NED
28	Rec	<2	edema, dermatitis, rash	2	46	no ^{□□}	97	yes / yes	alive, NED
29	Ad	<1	agranulocytosis, sepsis	4	52 [□]	yes	81	yes / yes	† (ca coli)
30	Ad	<1	edema, dermatitis, rash	2	1	yes	83	no	alive, NED

Follow-up refers to time from initiation of imatinib; NeAd = Neoadjuvant; Ad = adjuvant; Rec = recurrent disease; Pal = palliative
 PD = Persistent disease; NED = No evidence of disease at end of follow-up; ED = Evidence of disease; † = Dead
 □ interrupted for three years, restarted after recurrence; □□ (temporary) dose reduction

Supplemental Table A. Clinical details of the 30 patients with moderate, severe or life-threatening side effects from imatinib treatment.

Case no	Sex ♀/♂	Age	Treat- ment setting #	Primary location	Mitoses / 50 HPF	Tu- mour size (cm)	Metastatic spread	Risk classifica- tion	Mutation status	Surgery / margin
No metastatic disease										
1	♀	63	NeAd	duodenal	<1 [□]	3 ^{□□}	no	intermediate	KIT ex 11	radical / R0
2	♂	50	NeAd	rectal	8	3 ^{□□}	no	high	wild-type	radical / R0
3	♀	51	NeAd	small intestine	nd	17 ^{□□}	no	high	KIT ex 11	radical / R0
4	♀	82	Ad	small intestine	>10	8	no	high	nd	radical / R0
5	♀	75	Ad	rectal	nd	9	no	high	nd	intralesional / R1
6	♀	70	Ad	small intestine	<1	16	no	high	nd	intralesional / R1
7	♂	71	Ad	stomach	2	9	no	intermediate	nd	intralesional / R1
8	♂	68	Ad	stomach	>10	28	no	high	nd	radical / R0
9	♂	68	Ad	stomach	6	7	no	high	KIT ex 11	radical / R0
10	♂	65	Ad	small intestine	1	7	no	high	nd	radical / R0
11	♂	58	Ad	duodenal	4	8	no	high	nd	intralesional / R1
12	♂	60	Ad	stomach	5	11	no	high	nd	radical / R0
13	♀	54	Ad	stomach	5	15	no	high	PDGFRA	intralesional / R1
14	♀	55	Ad	small intestine	8	4	no	high	KIT ex 11	radical / R0
15	♀	54	Ad	stomach	1	22	no	high	KIT ex 11	radical / R0
16	♂	73	Ad	small intestine	5	10	no	high	nd	radical / R0
17	♂	75	Ad	stomach	nd	12 ^{□□}	no	high	KIT ex 11	radical / R0
Metastatic / Recurrent disease										
18	♀	71	NeAd	small intestine	1 [□]	12 ^{□□}	peritoneal	high	wild-type	tumor reduction / R2
19	♀	49	NeAd	duodenal	<10 [□]	11	hepatic	high	wild-type	intralesional / R1
20	♀	61	NeAd	cardia	23	7 ^{□□}	hepatic	high	KIT ex 11	radical / R0
21	♂	55	NeAd	stomach	nd	3 ^{□□}	hepatic, peritoneal	high	nd	radical / R0
22	♂	58	NeAd	small intestine	1-2 [□]	13 ^{□□}	hepatic	high	KIT ex 11	radical / R0
23	♂	63	NeAd	small intestine	0 [□]	10 ^{□□}	peritoneal	high	nd	radical / R0
24	♀	39	Pal	general	nd	nd	peritoneal	high	nd	tumor reduction / R2
25	♀	45	Pal	duodenal	>10	14	peritoneal	high	KIT ex 11	intralesional / R1
26	♀	60	Rec	stomach	nd	12	hepatic	high	nd	intralesional / R1
27	♀	66	Rec	small intestine	>4	7 ^{□□}	peritoneal	high	wild-type	intralesional / R1
28	♀	63	Rec	stomach	nd	7	peritoneal	high	KIT ex 11	intralesional / R1
29	♀	71	Ad	small intestine	nd	nd	peritoneal	high	KIT ex 11	intralesional / R1
30	♂	79	Ad	stomach	20	9	peritoneal	high	nd	radical / R0

NeAd = Neoadjuvant; Ad = adjuvant; Rec = recurrent disease; Pal = palliative; nd = not determined / no data available
[□] after (downstaging) treatment with imatinib, ^{□□} size based on x-ray.

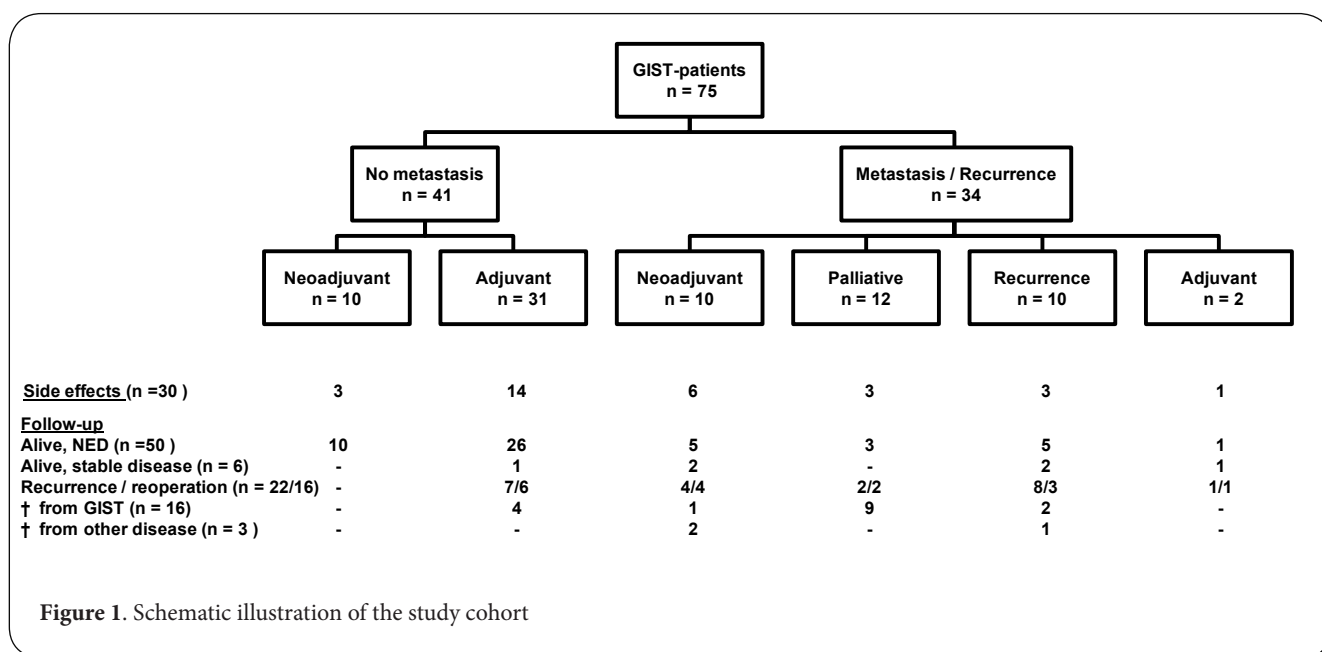


Figure 1. Schematic illustration of the study cohort

Association between side effects and favorable outcome

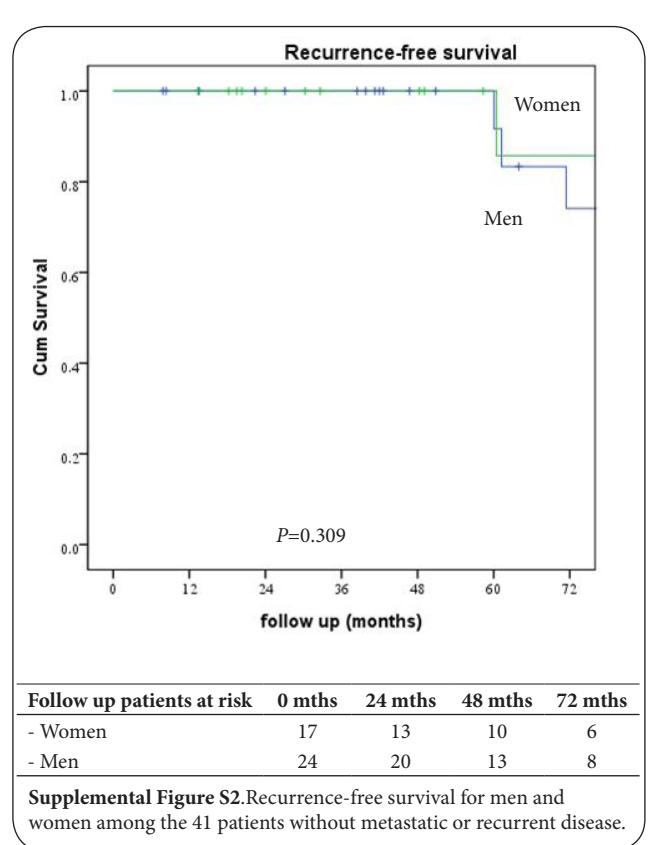
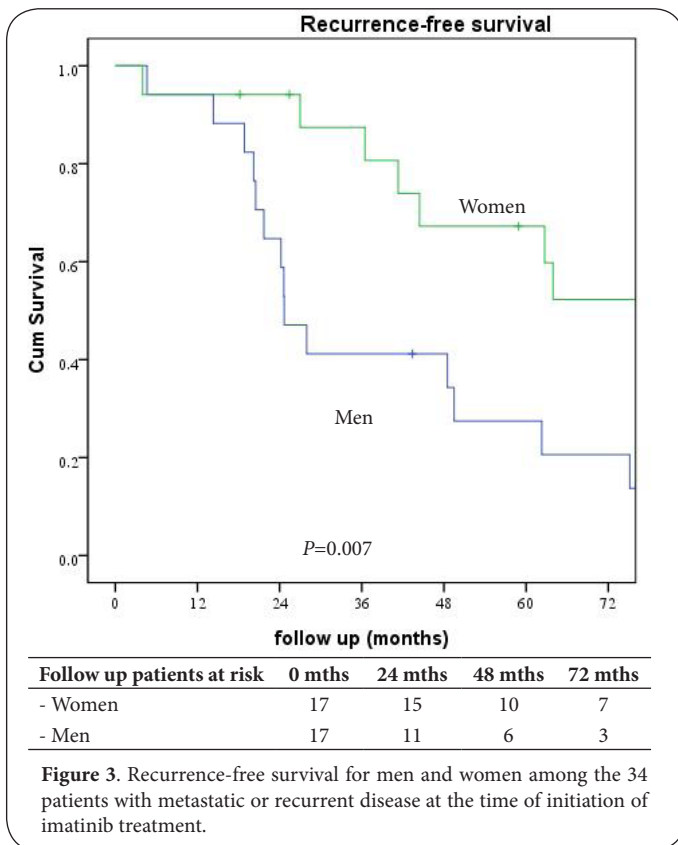
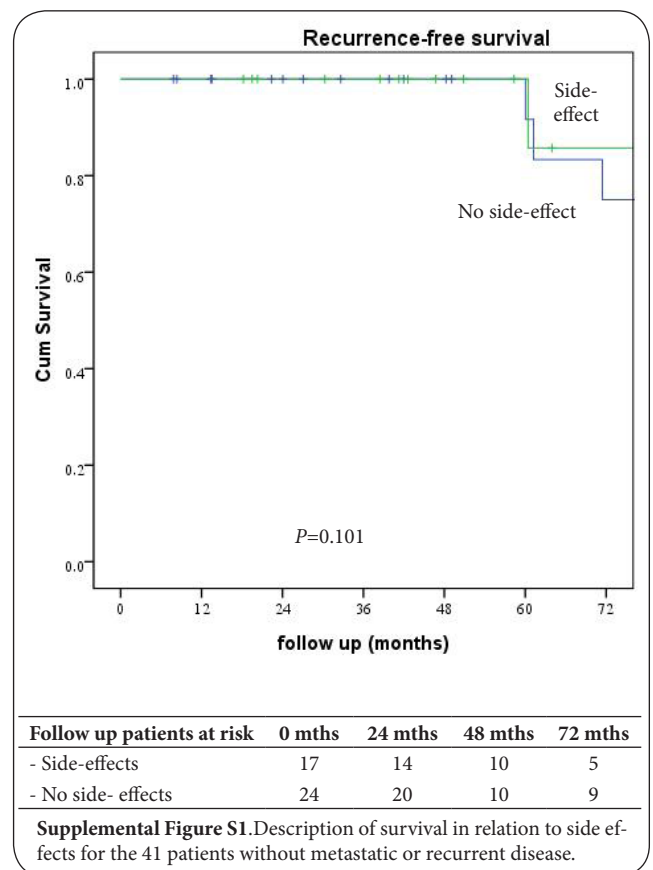
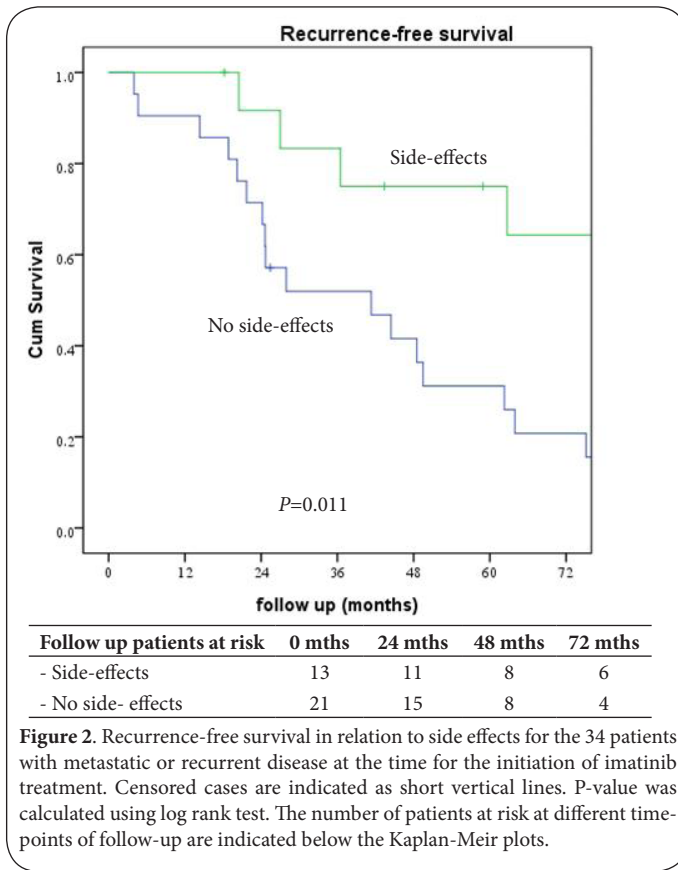
The presence of side-effects was found to be associated with a favorable recurrence-free survival for the group of patients with metastatic or recurrent GIST (log rank test; $P = 0.01$, Figure 2). No such differences were observed in the group of patients with localized disease, where the number of events was few (Supplemental Figure S1). The presence of side-effects was not found to be associated with differences in age, body weight, plasma albumin or creatinine clearance but there was a tendency to female dominance in the group of patients with metastatic or recurrent GIST ($P=0.078$), and female patients had a favorable recurrence-free survival ($P=0.01$, Figure 3). No differences in survival between men and women were found in the group of patients with localized disease (Supplemental Figure S2).

Discussion

The introduction of imatinib and other tyrosine kinase inhibitors has dramatically improved the prognosis for patients with high risk GIST. The treatment is generally considered to be well tolerated. However, recently attention has been drawn to a relatively high incidence of adverse events that may reduce the patient's adherence to and the clinical effectiveness of the imatinib treatment. It is important to be aware of the prevalence of side-effects and to offer supportive care to avoid interruption of treatment [16]. The objective of this retrospective study was to analyze the occurrence of moderate to severe or life-threatening side-effects and clinical outcome. Since some form of mild adverse event (*i.e.* grade 1) was reported in almost every case, we chose to limit our analysis to moderate-to-severe or life-threatening side-effects (grade 2 or higher), defined in accordance with the Common Terminology Criteria for Adverse

Events v4.0 (CTCAE). Forty percent of our patients complained of significant side-effects. For patients with metastatic or recurrent GIST, the presence of moderate to severe or life-threatening side-effects was associated with favorable recurrence-free survival. No such association was found for patients with localized GIST; however, for this group the strength of the analyses was limited by a relatively short follow-up time and few events.

The main weakness of this study is the lack of knowledge of the actual plasma concentration of imatinib. In GIST, higher exposure to imatinib has been found to predict a higher probability of therapeutic response, besides being correlated to the occurrence and number of side-effects [22]. However, determination of the plasma concentration of imatinib is still not used routinely in clinical practice and there are no practical guidelines for interpreting the concentration. A plasma concentration below 1,100 ng/mL has been associated with short time to disease progression in patients with unresectable/metastatic GIST [19]. The inter-patient variability in imatinib pharmacokinetics seems to be significant, and the trough level (C_{min}) has been significantly associated with albumin concentration, creatinine clearance and major gastrectomy but not to previous grades 3 to 4 toxicity in patients taken a standard dose of 400 mg daily [18]. Except for patients with *KIT* exon 9 mutations, 400 mg daily is the standard dose for treatment of high-risk GIST regardless of the patient's gender, age or body mass. A higher than standard dosage of imatinib has been associated with more severe side-effects [17]. However, Blanke *et al*; reported no significant difference in objective response for patients treated with high dose imatinib but, similar to our findings, a favorable outcome for female patients.



The observations of side effects and treatment response in GIST patients may be compared to similar studies in chronic myeloid leukemia (CML) for which imatinib treatment is the golden standard [23]. In CML, increased plasma concentrations of imatinib have been associated with a higher rate of complete molecular response [24]. In addition the plasma concentration was found associated with certain side effects [24]. Overall, slightly higher plasma concentrations were recorded in female compared to male patients [24]. Adherence to medication is another factor contributing to reduced treatment response and event free survival in CML [25,26]. In a study of pharmacy records for 4,043 patients reduced adherence to imatinib treatment was observed in CML as well as GIST patients [23,27].

While it is well established that patients with advanced GIST benefit from imatinib treatment, knowledge of how to optimize the dosage to obtain maximal effectiveness with a minimum of side-effects is limited. In this study we show that significant side effects from imatinib treatment are common and associated with a better outcome. This association likely reflects different plasma concentrations of imatinib. However, the lack of an association between body weight or BMI, plasma albumin or creatinine clearance and occurrence of side effects would argue against a simple dilution effect. Instead variations between patients related to factors such as adherence, drug absorption, pharmacokinetics and cellular uptake are expected to be of importance. Logically, the next step should be to perform a prospective follow-up study including plasma concentrations of imatinib and the main imatinib metabolites. Methods for the measurement of imatinib in plasma are currently not widely available for clinical practice. However, for the future, such methods are needed in order to evaluate how the plasma concentration of imatinib affects the event free survival and allow individualized tailoring of the dose to optimize outcome and minimize side-effects. Meanwhile our findings could be used in clinical practice in further supporting patients continued compliance to the medication when side effects are present. At the same time the patients have to be offered a close follow-up and proper management of side effects.

Conflict of interest

The authors declare that they have no conflict of interest.

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