Decrease of CD117 expression as possible prognostic marker for recurrence in the resected specimen after imatinib treatment in patients with initially unresectable gastrointestinal stromal tumors: a clinicopathological analysis

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Gastrointestinal stromal tumors (GIST) are the most common malignant mesenchymal tumors of the gastrointestinal tract. The principal treatment modality for primary GIST is surgery whereas for metastatic GIST, imatinib has an established role. In patients with locally advanced and metastatic GIST, the role of surgery in the imatinib era is still unclear. Fifteen patients with locally advanced ($n=9$) and/or metastatic GIST ($n=6$) were treated with imatinib followed by resection. Detailed histopathological examination was performed before and after treatment with imatinib, which was given for a median of 11 months before surgery. Ten patients showed a radiographic partial response, four patients had stable disease, and one patient progressed. At the time of surgery, the median tumor diameter was 6.5 cm. In all the nine patients with locally advanced GIST, a R0 resection could be performed. Histopathological examination showed imatinib effects in all tumors, including the case with progressive disease. All patients with locally advanced disease ($n=9$) were alive after a median follow-up of 40 months (range: 18–59), of which seven patients were free of disease. Four of the six patients treated for metastatic GIST died of disease after 30, 45, 50, and 74 months of follow-up. Remarkably, in five of six patients in whom CD117 expression was diminished or lost in the resection specimen, disease recurrence was observed. In patients with retained CD117 expression, one of the nine patients had recurrent disease. In conclusion, preoperative imatinib treatment in patients with locally advanced GIST resulted in a decrease of tumor load in most patients, enabling complete surgical resection. For patients with metastatic GIST, the role of surgery remains less clear. Loss or decrease of CD117 expression in the resected specimen after imatinib treatment may be associated with disease recurrence. *Anti-Cancer Drugs* 19:607–612 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms, which are believed to arise from the interstitial cells of Cajal [1,2]. The estimated prevalance is 15–20 per 1 000 000 persons [3,4]. Most GISTs express the tyrosine kinase (KIT) receptor, which can be detected immunohistochemically by the CD117 antibody [5,6]. Given the fact that the vast majority of GISTs are driven by KIT receptor activity, the development of a specific inhibitor of the KIT membrane receptor, imatinib (ST571, Gleevec, Glivec, Novartis, Basel, Switzerland) has resulted in an improved outcome for patients with locally advanced and metastatic GIST. Approximately 80% of patients with metastatic or locally advanced GIST benefit from imatinib therapy [7,8], with a median time to progression of 2 years [7]. However, further improvement of the treatment for locally advanced or metastatic GIST is needed. One means to achieve this may be through combining imatinib and surgery. Currently, the number of reports on the clinical outcome of patients with GIST treated with imatinib as induction therapy (either intended or unscheduled) and on the pathological response of the resected tumors is limited [9–13]. Furthermore, it is not well established if clinical response correlates with the histological response.

In the present study, the feasibility of performing surgery after imatinib treatment is analyzed in patients with locally advanced and/or metastatic GIST. In addition, pathological features of the preoperative specimens were compared with resected tumors.

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Methods

Information on all patients with locally advanced and/or metastatic or recurrent GIST who were treated with imatinib followed by surgical resection between April 2001 and January 2006 was collected. All patients were discussed in the Erasmus University Medical Center soft tissue sarcoma multidisciplinary team before starting the treatment. Imatinib was given daily at doses of 400–800 mg. In patients with locally advanced disease without metastases on computed tomography (CT) scanning, a positron emission tomography scan was performed before imatinib therapy and after a median interval of 3 weeks to evaluate tumor response to imatinib. In all patients, response to therapy was evaluated by CT scan every 2 or 3 months. Response was assessed according to Response Evaluation Criteria in Solid Tumors [14]. Imatinib was continued until a 'maximal response' was attained, defined as two consecutive CT scans not showing further regression or, in the case of locally advanced disease without metastases, until the surgeon deemed a radical resection possible, whichever condition was attained first. As it is not known if surgery influences survival in this group of patients, survival was calculated from the start of imatinib administration.

Preoperative biopsies and resected specimens were evaluated by routine histological examination. Recorded parameters included tumor diameter, resection margins, immunohistochemical staining intensity for CD117 and CD34, tumor cellularity, mitotic activity, aspect of the stroma, and presence of necrosis. Tumors were stained for CD117 and CD34 (all antibodies and detection system were provided by DAKO, Glostrup, Denmark), no antigen retrieval method was used for CD117 staining. The staining intensity and amount of cells stained were qualitatively assessed.

Results

Patients

Between April 2001 and January 2006, 15 patients (11 males and four females), with a median age of 57 years (range: 30–78 years), with locally advanced and/or metastatic GISTs were treated with imatinib followed by surgical resection. During this period, a total of 118 GIST patients were treated with imatinib. So the study population involves 12.7% of the total imatinib-treated patient population for the indicated period. Twelve patients had locally advanced disease, of which three patients also had distant metastases. Three patients had locally recurrent disease, of which two also had distant metastases. In eight patients the primary tumor was located in the stomach; in four patients the tumor was located in the rectum; in two patients in the small bowel; and in one patient in the omentum.

Imatinib and surgery

Imatinib was administered at a starting dose of 400 mg ($n = 12$), 600 mg ($n = 1$), or 800 mg ($n = 2$) daily. In one patient, the daily dose was increased to 600 mg and in two patients, to 800 mg daily after first progression. Dose elevation occurred after 5, 6, and 6 months, respectively. Eventually, this dose elevation resulted in one partial response, one stable disease, and one progression of disease. Preoperative imatinib was given for a median time of 11 months (range: 2–42 months). All patient characteristics are summarized in Table 1.

As stated earlier, one patient (7%) had progressive disease after 14 months, despite increasing imatinib to 800 mg daily. Despite this, surgery was considered because of local symptoms of the gastric tumor. A partial remission was recorded in 10 patients and stable disease in four patients. Three patients with stable disease underwent surgery because there were clinical shrinkage of the

Table 1 Tumor site, imatinib dose, response and survival characteristics of the 15 patients with GISTs

Patient no.	Dose of imatinib (mg)	Tumor site	Reason for the use of imatinib	Response after imatinib therapy	Type of resection	Adjuvant imatinib	Overall survival (months) and disease status
1	400/600	Omentum	M	PR	R1	Yes	30 DD
2	600/800	Small bowel	M	SD	R2	Yes	74 DD
3	400	Stomach	M	PR	R1	No	47 AD
4	400	Rectum	LA	PR	R0	No	47 ND
5	400	Stomach	LA	SD	R1	Yes	46 AD
6	400	Rectum	LA	PR	R0	No	41 ND
7	400	Small bowel	LA + M	PR	R1	Yes	46 ND
8	800	Rectum	LA	PR	R0	No	59 ND
9	400/800	Stomach	LA + M	PD	R0	Yes	50 DD
10	800	Stomach	LA + M	SD	R0	–	45 POD
11	400	Stomach	LA	PR	R0	Yes	22 ND
12	400	Stomach	LA	SD	R0	Yes	18 ND
13	400	Rectum	LA	PR	R0	Yes	27 AD
14	400	Stomach	LA	PR	R0	Yes	40 ND
15	400	Stomach	LA	PR	R0	Yes	29 ND

AD, alive with disease; DD, died of disease; LA, locally advanced; M, metastatic disease; ND, no evidence of disease; PD, progressive disease; POD, perioperative death; PR, partial response; R, resection; SD, stable disease.

tumors; however, the tumors showed less than 50% reduction at radiological assessment. One patient with stable disease developed severe obstruction owing to metastases in the small intestine and has undergone surgery.

Histopathology of resected tumors

In ten patients a R0 resection (10/15), in four patients a R1 resection (4/15), and in a single patient a R2 resection (1/15) were achieved. At resection, the median tumor diameter was 6.5 cm (range: 1.5–15 cm). In all nine patients with locally advanced GIST, a R0 resection could be performed. Histopathological analysis, summarized in Table 2, showed treatment effects in all specimens, including in the single specimen from the patients with progressive disease. The most prominent feature was stromal hyalinization. In addition, there was a change in the cell–stroma ratio with tumors becoming markedly hypocellular after imatinib treatment.

CD117 expression was confirmed in 14 tumors before systemic therapy; in a single case, no tissue was available for examination before imatinib administration; however, the resected specimen was CD117 positive. All pretreatment tumor specimens showed strong universal staining in all or most tumor cells. In six patients, there was a weakening of CD117 expression in the resected specimen. Although most tumor cells still showed cytoplasmic staining, the intensity was clearly diminished in comparison to the prechemotherapy-treated specimens.

Follow-up

All patients with metastatic disease continued imatinib treatment after surgery until progression. All patients with locally advanced disease continued imatinib for 1 year.

At the time of analysis, the median follow-up time after starting imatinib was 45 months (range: 18–74 months), and the median time after surgery was 18 months (range: 3–33 months).

All nine patients with only locally advanced disease were alive after a median follow-up of 40 months (range: 18–59 months, from the start of imatinib administration), seven of these patients without evidence of disease. Four of the six patients treated for metastatic disease died after 30, 45, 50, and 74 months of follow-up. Two other patients were alive after 46 months with disease and 47 months without evidence of disease, respectively.

All six patients with reduced CD117 expression (with locally advanced disease and/or metastases), except one, had recurrent disease after a median of 13 months. In patients with retained CD117 expression, only one of the nine patients had recurrent disease after 31 months.

Discussion

Even after the advent of imatinib, the role of surgery in patients with primary resectable GIST is unchanged and surgical resection remains the gold standard. Currently, three randomized trials are being conducted to evaluate the value of adjuvant imatinib in patients after resection (European Organization for Research and Treatment of Cancer, the American College of Surgeons Oncology group, and GERMANY/SSG) and results with respect to overall survival are eagerly awaited. The role of surgery

Table 2 Gastrointestinal stromal tumors pre/postimatinib pathology

	Cellularity		Stroma		Cell–stroma ratio		CD117		CD34		Mitoses	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	3	3	NS	NS	3	3	+	−/+	+	−	29/25 HPF	4
2	2	3 (focal)	NS	H (focal)	2	2	+	−/+	+	+	8	3
3	3	3 (focal)	NS	H	3	1	+	−	ND	−	1 (40 HPF)	9
4	NA	3	NA	H	NA	3	NA	+	NA	+	NA	1
5	3	1	NS	H	3	1	+	+	+	+	19	0
6	3	3	NS	NS	3	3	+	+	+	+	1	1
7	3	3 (focal)	NS	H	3	2	+	+	−	−	ND (insufficient)	0
8	3	3	NS	H/E (cystic degeneration)	3	3	+	+	ND	+	ND (insufficient)	1
9	3	3 (focal)	NS	H/E (cystic degeneration)	3	2	+	+	+	+	ND (insufficient)	24
10	3	3	NS	H/E	3	3	+	+/−	ND	+	31	27
11	3	1	NS	H	3	1	+	+	+	+	ND (insufficient)	0
12	3	2	NS	H	3	1	+	+	+	+	3 (8 HPF)	1
13	3	2 (3 focal)	NS	H/E	3	1	+	−	+	+	0 (25 HPF)	0 (25 HPF)
14	3	1 (focal)	NS	H/E	3	1	+	−/+	+	−	ND (insufficient)	0
15	3	1 (2 focal)	NS	H	3	1	+	+	+	+	0 (20 HPF)	1 (5 HPF)

Cellularity (tumor cells): 1, low; 2, medium; 3, high (judged on cellular parts).
Stroma: E, edematous; H, hyalinized; NS, nonspecific.
Cell–stroma ratio: 1, stroma ≫ cells; 2, stroma = cells; 3, cells ≫ stroma.
CD117 stain: +, pos; +/−, moderate; −/+, weak; −, negative.
CD34 stain: +, pos; +/−, moderate; −/+, weak; −, negative.
HPF, high-power field; NA, not available; ND, not done.

Table 3 Outcome of induction treatment with imatinib followed by surgical resection of locally advanced and/or metastatic gastrointestinal stromal tumors

Authors	LA or M/R	FU (median/months)	R0	Survival
Andtbacka *et al.* [19]	LA ($n=11$)	19.5	100%	All alive at last FU
	M/R ($n=35$)	30.7 (R0)	31%	All alive at last FU
		11.8 (R1/2)	0%	79% alive at last FU
Bonvalot *et al.* [20]	LA ($n=5$)	32[a]	100%	62% 2 years survival[a]
	M/R ($n=17$)		59%	
Raut *et al.* [21][b]	LA ($n=9$)	14.6[a]	SD 78%	95% 1 year survival
	M/R ($n=60$)		LD 25%	86% 1 year survival
			GD 7%	0% 1 year survival
Rutkowski *et al.* [22][c]	LA ($n=3$)	11.5 (group 1)	Group1 50%	All alive at last FU
	M/R ($n=29$)	12 (group 2)	Group 20%	62.5% alive at last FU
Gronchi *et al.* [10][d]	LA ($n=3$)	21 (group A)	100%	All alive at last FU
	M/R ($n=35$)	29 (group B)	89%	All alive at last FU
		12 (group C)	50%	60% alive at last FU
DeMatteo *et al.* [9][e]	M/R ($n=40$)	20 (RD)	85%	100% 2 years
		13 (FR)	46%	36% 2 years
		7 (MR)	29%	36% 1 year
Present series	LA ($n=9$)	40	89%	All alive at last FU
	M/R ($n=6$)	46	33%	33% alive at last FU

FR, focal resistance; FU, follow-up; GD, generalized disease progression; LA, locally advanced disease (without evidence of metastases); LD, limited progression disease; MR, multifocal resistance; M/R, metastatic or recurrent disease; R0, % macroscopic complete surgical resection; RD, responsive disease; SD, stable disease.
[a]LA and M/R.
[b]In this study, patients were divided into three categories: SD, LD, and GD progressions.
[c]In this study, patients were divided into two groups: group 1, points with LA/M/R disease that showed good response and group 2, points with LA/M/R disease that showed partial response or stable disease, however, at last imaging progression of disease; salvage therapy.
[d]In this study, patients were divided into three groups: group A, LA disease; group B, points with M/R without progression; and group C, points with M/R with primary or secondary resistance.
[e]In this study, patients were divided into three groups: RD, FR, and MR.

after imatinib in locally advanced or metastatic disease seems more controversial.

Locally advanced gastrointestinal stromal tumors

Defining locally advanced GIST is problematic, as it is debatable whether size or growth into adjacent organs typifies a tumor as being locally advanced. As GIST is generally an expansive and not an infiltrative tumor, actual parenchymal infiltration in adjacent organs occurs only in a minority of cases [15]. Therefore, most authors consider size as the primary determinant for locally advanced disease. In the preimatinib era, complete resection of a large (i.e. locally advanced) primary GIST was only achieved in 50% of cases [16]. As completeness of resection of the primary tumor (R0 vs. R1 or R2) seems to significantly influence GIST prognosis, it follows that larger tumors will carry a worse prognosis, even if surgery is technically feasible [17]. Additionally, large tumors carry an increased risk of tumor rupture owing to the demanding technical procedure and manipulation during surgery. It has been demonstrated that tumor rupture has a detrimental effect on survival, even in cases in which the resection is considered complete [18]. Therefore, if a GIST is locally advanced, imatinib treatment is often used with the aim to increase the chances of a R0 resection and to decrease the risk of tumor perforation during surgery. However, it should be noted that a survival benefit has not been shown in a randomized controlled study. In our series, eight of nine patients with locally advanced disease underwent a R0 resection and tumor rupture occurred in a single patient with a R1 resection. In addition, data from previously reported retrospective series, summarized in Table 3, seem to support the described approach for patients with locally advanced GISTs [19,20].

Metastatic gastrointestinal stromal tumors

The development of secondary resistance, the major limitation of an active drug such as imatinib, is a reason why surgery of residual disease is considered in some institutions that aim to maximize the reduction of tumor burden and prolong the time to secondary resistance. The observation from the published phase III study comparing 400–800 mg imatinib that disease burden (of tumor bulk) predicted secondary resistance [23], further supports the approach to resect residual disease. However, there is a lack of formal evidence for the role of surgery at this stage of the disease. To date, surgical resection for recurrent or metastatic GIST has been limited mainly to selected patients with single-site disease or multiple small lesions (e.g. low-volume peritoneal surface foci) [24]. Multiple intra-abdominal organ resection and tumor debulking have not generally been performed, except in exceptional cases for palliation of symptoms in patients with an otherwise good performance status. Recently, some authors have suggested that resection of metastatic GIST lesions may also be performed in an effort to keep disease under control. In the study by Raut *et al.* [21] in patients with metastatic GIST becoming resectable after induction therapy with imatinib, a 95% 1-year survival and an 80% 1-year progression-free survival were reported. Rutkowski *et al.* [22] reported similar results with all patients being alive and 87.5% disease-free after a median follow-up of 11.5 months. In a study by Gronchi

et al. [10], long-term survival was observed after surgery, especially in patients with a favorable response to imatinib. These studies support the development of a randomized controlled trial for patients with metastatic GIST (Table 3). The European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma group is preparing a trial, in which patients with metastatic disease will initially receive imatinib and after 6 months will be randomized to undergo resection of all visible tumors followed by continuing imatinib, versus imatinib therapy only. The continuation of imatinib in all patients in this study is based on a recently published study indicating that discontinuing imatinib is detrimental to tumor control [25].

Pathology

At diagnosis, CD117 expression was observed in all tested patients, which is in accordance with the literature (95% expression). By contrast, six of the 15 patients showed no or reduced CD117 expression after imatinib therapy. Remarkably, five of these six patients with reduced CD117 expression had recurrent disease after a median interval of 13 months, whereas only one of the nine patients with sustained CD117 expression had recurrent disease after 31 months. This suggests that reduced CD117 expression after imatinib therapy may serve as a predictor of progression in GIST. Obviously, this observation requires validation in a larger patient population. The histopathological changes of GIST after imatinib therapy are currently poorly documented in the literature. Haller *et al.* [12], in concordance with our observation, observed hypocellular stroma with weakening of KIT expression in a resection specimen from a patient treated with imatinib followed by surgery for a locally advanced GIST. Agaram *et al.* [11] correlated the histopathology of resected specimens with the clinical response after imatinib treatment. All specimens, as in our study, showed imatinib effects with stromal hyalinization being the most prominent. The histological response of GIST to imatinib therapy was variable and heterogeneous. The results did not correlate with duration of the imatinib therapy and size of the tumor. Furthermore, there was no consistent correlation with the response to imatinib and the intensity and extent of staining of KIT in the resected specimen. However, the postimatinib histology was not compared with preimatinib tissue, precluding conclusions on effects of KIT expression.

Why tumors lacking cytokine-KIT (c-KIT) expression after previous treatment with imatinib may bear a higher risk to relapse, as is suggested in this small series, remains to be established. In untreated primary GIST tumors, the lack of c-kit expression is not associated with outcome [15,26]. However, it may be possible that in imatinib-treated tumors, a c-kit-negative phenotype is associated with particular mutations in the c-kit gene, thus resulting in a higher risk to relapse. The number of patients included in this study is too small to assess this.

In conclusion, preoperative imatinib treatment in patients with locally advanced GIST resulted in a decrease of tumor load in most patients, thereby enabling complete surgical resection without tumor rupture, which in turn resulted in long-term survival. For patients with metastatic and/or recurrent GIST, the beneficial role of surgery is less clear and has to be assessed in randomized trials. In addition, loss or weakening of CD117 expression in the resected specimen after imatinib treatment may be associated with disease recurrence.

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