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ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Neoadjuvant Imatinib in Locally Advanced Gastrointestinal Stromal Tumors (GIST): The EORTC STBSG Experience

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ABSTRACT

Background. Preoperative imatinib therapy of locally advanced GIST may facilitate resection and decrease morbidity of the procedure.

Methods. We have pooled databases from 10 EORTC STBSG sarcoma centers and analyzed disease-free survival (DFS) and disease-specific survival (DSS) in 161 patients with locally advanced, nonmetastatic GISTs who received neoadjuvant imatinib. OS was calculated from start of imatinib therapy for locally advanced disease until death or last follow-up (FU) after resection of the GIST. DFS was calculated from date of resection to date of disease recurrence or last FU. Median FU time was 46 months.

Results. The primary tumor was located in the stomach (55 %), followed by rectum (20 %), duodenum (10 %), ileum/jejunum/other (11 %), and esophagus (3 %). The tumor resection after preoperative imatinib (median time on therapy, 40 weeks) was R0 in 83 %. Only two patients have demonstrated disease progression during neoadjuvant therapy. Five-year DSS/DFS rates were 95/65 %, respectively, median OS was 104 months, and median DFS was not reached. There were 56 % of patients who continued imatinib after resection. Thirty-seven GIST recurrences were diagnosed (only 5 local relapses). The most common mutations affected exon 11 *KIT* (65 %). Poorer DFS was related to primary tumor location in small bowel and lack of postoperative therapy with imatinib.

Conclusions. Our analysis comprising the largest group of GIST patients treated with neoadjuvant imatinib in routine practice indicates excellent long-term results of combined therapy in locally advanced GISTs.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of digestive tract. Radical surgery is the treatment of choice in primary resectable gastrointestinal stromal tumors, but virtually all GISTs are associated with a risk of recurrence and approximately 40–50 % of patients with potentially curative resections develop recurrent or metastatic disease.[13,33] The advances in the understanding of molecular mechanisms of GIST pathogenesis have resulted in the development of a treatment modality, which has become a model of targeted therapy. Imatinib mesylate has revolutionized the therapy of advanced GISTs and was the first effective, worldwide-approved nonsurgical treatment for inoperable and/or metastatic cases.[2,8,39] Imatinib also has been approved for adjuvant therapy in patients after resection of primary GIST with significant risk of recurrence.[7,22,23] The spectacular response to imatinib therapy in metastatic setting has led to the development of preoperative treatment strategy to facilitate resection and decrease morbidity of the surgical procedure by reducing the need for extensive, multiorgan resections, and diminishing the peroperative risk of tumor rupture and thus spill of active tumor cells.[24,25] In selected cases of locally advanced GISTs, the strategy of neoadjuvant imatinib therapy has become a common approach.[10,15,38] However, the formal evidence from clinical trials of utility and outcome of neoadjuvant therapy with imatinib is limited.[11,18,19,21,30] Moreover, the numbers of patients in series presented were limited [1,5,12,14,16,27–29,32,35,36,41] and often mixed with metastatic GIST operated for residual disease. Furthermore, the long-term outcome of a neoadjuvant strategy in terms of disease recurrences and survival is unknown.

The purpose of this study was to assess the long-term results of preoperative therapy given to patients with locally advanced GISTs based on large multinational data set.

METHODS

We have performed a pooled analysis of databases of ten EORTC (European Organisation for Research and Treatment of Cancer) Soft Tissue and Bone Sarcoma Group (STBSG) centers in 161 patients with locally advanced, nonmetastatic GISTs who received neoadjuvant imatinib therapy. All consecutive patients treated between 2002 and 2011 were included. The diagnosis of GIST was confirmed histologically in all cases and by immunohistochemical staining for CD117. All patients were treated with imatinib in initial licensed dose of 400 mg daily. The treatment was continued to resection of the tumor or confirmed disease progression. Imatinib was continued until a "maximal response" was attained, defined as two consecutive CT scans not showing further regression or, if the surgeon deemed a radical and/or organ-sparing resection possible, whichever condition was attained first. Postoperative treatment with imatinib was continued at the discretion of the attending physician. The objective response of GIST to imatinib therapy was evaluated with serial computed tomography (CT) examinations. Patients did not undergo any further selection. Mutational analysis of *KIT* (exons 9, 11, 13, and 17) and platelet-derived growth factor receptor alpha (*PDGFR-α*, exons 12, 14, and 18) was performed in 115 cases (71.4 %) based on DNA isolated from paraffin-embedded or fresh frozen tumor tissue. All patients were followed and during follow-up, we analyzed the incidence and pattern of disease recurrences and survival of the patients.

Statistical Analysis

Disease-free survival (DFS) was calculated from the date of primary tumor resection to the date of recurrence or the last follow-up date. Disease-free survival was assessed with respect to the following variables: demographic data (age at diagnosis $\leq$45 vs. >45 years, and sex), primary tumor site (gastric vs. duodenum vs. jejunum/ileum vs. large bowel vs. others), type of surgical resection (R0: microscopically radical resection vs. R1: microscopically nonradical, but macroscopically radical resection or tumor intraoperative rupture), molecular findings (*KIT* exon 11 mutants vs. others), postoperative (adjuvant) therapy with imatinib for minimum 12 months (yes vs. no). Overall survival (OS) and disease-specific survival (DSS) time was calculated from the date of the first imatinib administration for locally advanced disease until last follow-up or death after resection of the GIST. All deaths from other causes than GIST-related were recorded as censored for DSS calculations. All statistical analyses were performed using and Statistica software, version 7.1 (Statsoft®; Tulsa, OK). For the survival analysis, Kaplan–Meier estimates were used with generalized Wilcoxon and the log-rank tests for bivariate comparisons. Differences were considered statistically significant if p values were <0.05.

RESULTS

Clinicopathological and Surgical Data

All patients were followed up for a median of 46 months. There were 69 female and 92 male patients, with a median age of 61 years. The detailed distribution of

TABLE 1 Characteristics of 161 patients with primary locally advanced GISTs treated with neoadjuvant imatinib

Clinicopathological feature		Total no (%) 161
Age (year)	Median (range)	61 (35–84)
Gender	Female	69 (43 %)
	Male	92 (57 %)
Primary tumor site	Stomach	89 (55.3 %)
	Duodenum	16 (9.9 %)
	Small bowel (ileum/jejunum)	15 (9.3 %)
	Rectum	33 (20.5 %)
	Esophagus	5 (3.1 %)
	Other or intraperitoneally with unknown primary origin	3 (1.9 %)
Type of surgical resection	R0	134 (83.2 %)
	R1	27 (16.8 %)
Mutational status[a]	KIT exon 11 mutation	74 (64.9 %)
	KIT exon 9 mutation	12 (10.5 %)
	PDGFRA exon 12	2 (1.8 %)
	PDGFRA exon 18	8 (7 %)
	Wild-type	18 (15.8 %)
Postoperative imatinib therapy (minimum 1 year)	Yes	91 (56 %)
	No	70 (44 %)
Patients distribution	Erasmus MC Cancer Institute Rotterdam and Radboud University of Nijmegen, the Netherlands	40 (24.8 %)
	Netherlands Cancer Institute; Amsterdam, the Netherlands	34 (21.1 %)
	National Cancer Institute; Milan, Italy	20 (12.4 %)
	Maria Sklodowska-Curie Memorial Cancer Center; Warsaw, Poland	11 (6.8 %)
	University Hospitals Leuven, KU Leuven, Leuven; Belgium	7 (4.3 %)
	University of Mannheim, Germany	20 (12.5 %)
	Institute Gustave-Roussy, Paris, France	16 (10 %)
	University of Essen, Germany	5 (3.1 %)
	Institute Bergonie; Bordeaux, France	8 (5 %)

[a] Mutational status was available in 114 cases

R0 microscopically radical resection; *R1* microscopically nonradical but macroscopically radical resection or intraoperative tumor rupture

clinical and pathological data of patients included in the study is listed in Table 1. The majority of primary tumors were located in the stomach (55.3 %), followed by rectum (20.5 %), duodenum (9.9 %), ileum/jejunum (9.3 %), esophagus (3.1 %), and other (1.9 %). The most common mutation affected exon 11 *KIT,* which was observed in 65 % of tumors.

The median time of preoperative imatinib therapy was 40 weeks (range 6–190). There were 129 patients who had a documented response to preoperative imatinib (80.1 %), and 30 patients demonstrated stabilization of disease before surgery (18.6 %).

The histologically assessed margin status of tumor resection after preoperative imatinib therapy was R0 in 83.2 % of cases. Postoperative complications were recorded in 15 % of cases, but only 3 % required surgical intervention. One patient died in postoperatively after total gastrectomy. Ninety-one patients (56 %) continued imatinib postoperatively for at least 1 year. The median duration of adjuvant imatinib therapy was 19 months (range 12–76).

Disease Recurrences and Survival

Only two patients demonstrated disease progression during neoadjuvant therapy. During follow-up, we detected 37 disease recurrences (23 %); only five (3 %) were local recurrences, and the others were intraperitoneal dissemination and/or liver metastases. The median DFS time after resection of primary GIST was not reached, and the estimated 5-year DFS rate was 65 % (95 % confidence interval [CI] 59.1–70.9 %; Fig. 1a). Twenty-four patients died during follow-up but only 12 due to disease progression. Five-year OS and DSS rates from start of imatinib therapy were 87 % (95 % CI 78–98 %) and 95 % (95 % CI

80–99 %; Fig. 1b), respectively. Median OS was 104 months; it has not been reached for DSS.

Univariate Analysis for DFS

In bivariate analysis, the following factors demonstrated positive impact on DFS: use of postoperative therapy with imatinib ($p = 0.04$; Fig. 2a) and primary tumor location outside jejunum/ileum ($p = 0.006$; Fig. 2b).

Five-year DFS rate in patients treated with adjuvant imatinib was 72 % versus 57 % for patients not receiving imatinib postoperatively. Poorer DFS also was related to primary tumor location in the small bowel. The 3-year DFS rate after resection of the tumor was only 52 % for primary tumors related in jejunum/ileum compared with 78 % months for duodenal GIST, 83 % for gastric GISTs, and 88 % for rectal GISTs (Fig. 3).

DISCUSSION

Our analysis comprises the largest group of GIST patients treated with neoadjuvant imatinib in routine practice indicates excellent long-term results of combined therapy in locally advanced GISTs. The preoperative use of imatinib appears beneficial for selected patients with locally advanced or marginally resectable primary GIST. Consideration of cytoreduction with imatinib may facilitate R0 resection (which was achieved in more 80 % of cases in the present series) and organ-sparing surgery.[20] Moreover, because primary tumors are fragile and hypervascular,

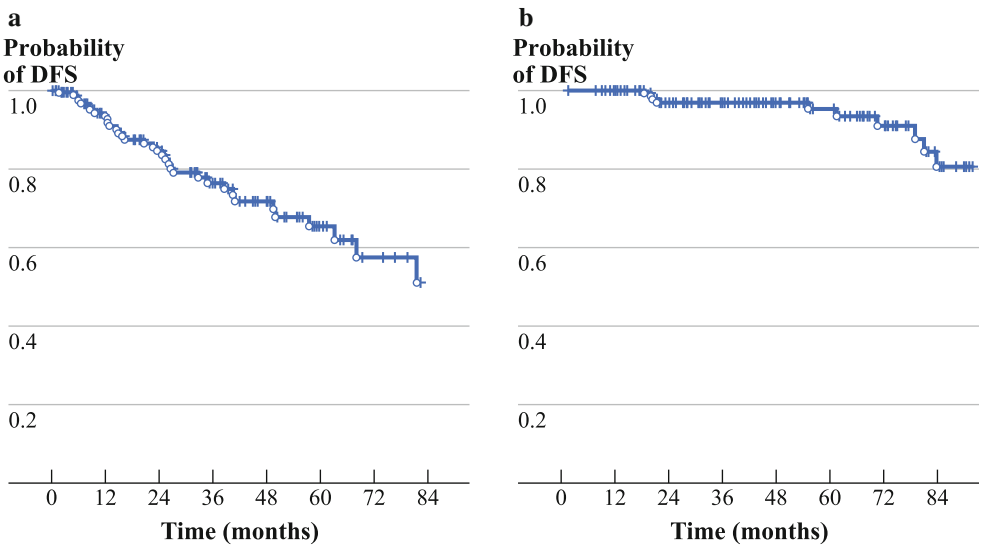

FIG. 1 **a** Disease-free survival after resection of GIST treated preoperatively with imatinib (from date of radical surgery). **b** Disease-specific survival from date of start of preoperative imatinib therapy

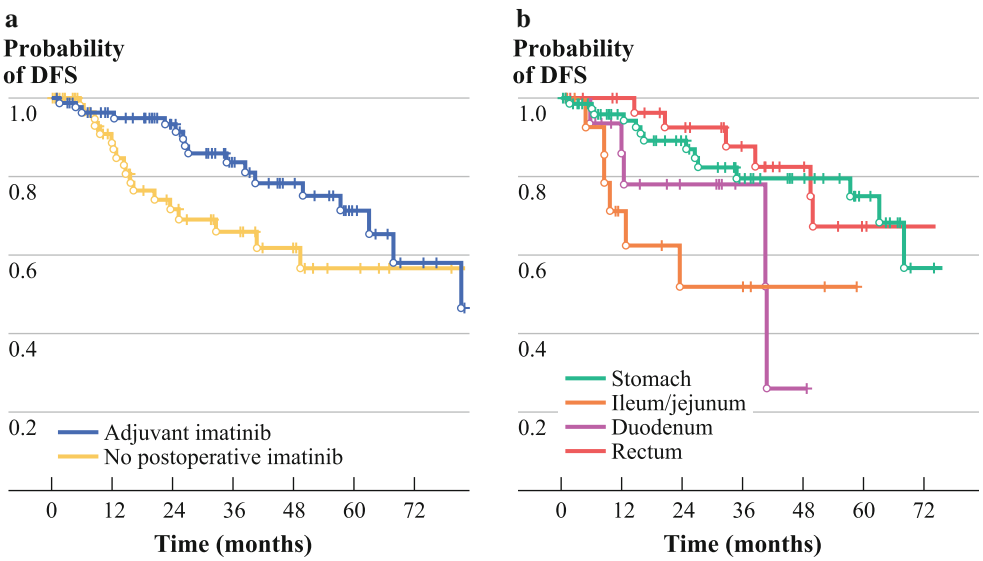

FIG. 2 **a** Disease-free survival according to use of postoperative imatinib (from date of radical surgery). **b** Disease-free survival according to primary tumor location (from date of radical surgery)

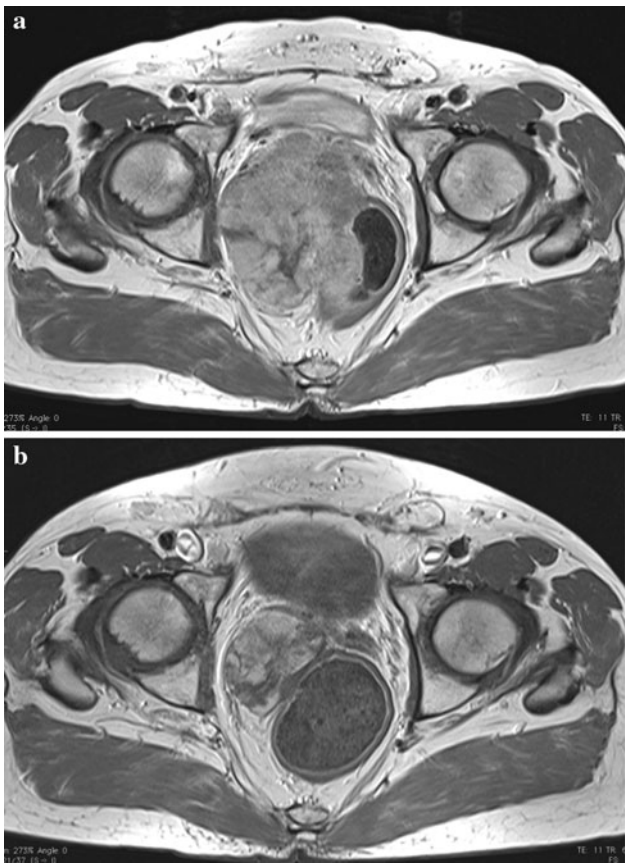

FIG. 3 Magnetic resonance imaging of rectal GIST treated preoperatively with imatinib for 8 months, where tumor shrinkage allowed radical local excision of the tumor with sparing of the rectum function (**a** initial tumor, **b** tumor after 8 months of neoadjuvant imatinib)

preoperative imatinib therapy may decrease the risk of bleeding, postoperative complications, or tumor rupture (the latter is related to high probability of tumor dissemination).[15,17] This kind of approach is recommended by current ESMO and NCCN guidelines [31,37] but until now supported by small nonrandomized clinical trials or small series of patients.

The prospective trial sponsored by Radiation Therapy Oncology Group (RTOG), the National Cancer Institute, and the American College of Radiology Imaging Network (ACRIN)—RTOG S-0132/ACRIN 6665 evaluated the role of preoperative imatinib 600 mg daily for 8–12 weeks combined with planned surgery followed by 2 years of adjuvant imatinib.[11] It included 31 patients with primary, localized GIST, and it demonstrated 5-year PFS and OS rates of 57 and 77 %. However, a high percentage of patients experienced disease progression after discontinuation of 2-year adjuvant imatinib therapy.[40] The largest trial of preoperative imatinib (given for 6 months) was German phase II CST1571-BDE43 study, which confirmed (data presented during Annual ASCO 2012 meeting) that only one patient was inoperable at planned surgery and 26 of 41 (64 %) had less extensive surgery compared with the resection that was initially planned.[21] These results imply that administration of imatinib preoperatively improves the possibility of complete excision of the tumor with substantial decrease of the need for removal of surrounding organs or formal organ resections.

The candidates for preoperative imatinib are those patients who may benefit from tumor downstaging before operation, where it is anticipated that initial surgery will be mutilating anticipated or where a high probability of intraoperative tumor rupture/blood loss exists. Such selection process requires careful multidisciplinary assessment. This strategy is especially attractive in difficult locations (distal rectum, esophagus, gastroesophageal junction, or duodenum) where resection of the primary tumor may cause significant morbidity or functional deficits. In our study rectal and duodenal GIST comprised more than 30 % of whole cohort, which is much higher than in the general GIST population. Proper selection of candidates for neoadjuvant therapy ideally also should include tumor genotyping based on preoperative biopsy, what is recommended as obligatory in the latest ESMO guidelines [37], although sometimes it can be difficult on a small biopsy specimen. Genotyping allows for the administration of imatinib to patients who have the highest chance to respond. Imatinib sensitivity is closely related to sensitive tumor mutations in *KIT* exon 11 and *PDGFRA* non-D842 V. In cases of confirmed *KIT* exon 9 mutations, a higher dose of imatinib (800 mg daily) should be considered because available data has shown that the response of GISTs with exon 9 *KIT* mutations depends on the dose of the drug and that using higher doses of imatinib leads to significant improvement of progression-free survival.[6]

The optimal duration of preoperative therapy usually ranges from 4 to 12 months to achieve a maximal dimensional response to imatinib. This is the time when a plateau in tumor shrinkage is usually seen and the risk of developing secondary resistance to therapy is still very low.[4,16,26] Careful response assessment should be undertaken not to miss the best timing for surgery. There also is clear evidence that imatinib therapy in primary advanced disease should lead to resection of the tumor and cannot replace surgery.[3] demonstrated that patients with potentially resectable GIST treated with imatinib alone (who did not undergo surgery) had poorer PSF and OS comparable to those treated in metastatic setting. We also have confirmed that preoperative therapy with imatinib is a safe option; only 3 % of patients had complications that required earlier surgical intervention.

More than 80 % of cases in our series demonstrated response to imatinib therapy, which is comparable to the data of Doyon et al. [9] and Goh et al. [14]. Although, no complete responses were observed in our study, more than 80 % patients

had enough response to devitalize the tumor and to allow resection with microscopically clear margins. The number of partial responses in our patients is higher compared with that of phase II RTOG 0132 trial,[11] which is probably related to short duration of preoperative imatinib (for a maximum of 12 weeks) in that trial in contrast to our series where median duration of preoperative imatinib was 40 weeks.

We have shown excellent long-term, progression-free and disease-specific survival, which also may be related to the fact that more than 50 % of patients received adjuvant therapy with imatinib for at least 1 year. Because the majority of GISTs treated with preoperative imatinib belong to high- or intermediate-risk tumors, who are candidates for adjuvant therapy anyway (at least based on assessment of primary tumor size and location; as the initial tru-cut biopsy can be inconclusive in terms of evaluation of mitotic index), patients should be treated with postoperative imatinib. We have found a significant difference in DFS in favor of patients receiving imatinib postoperatively. It is especially true for small-bowel GISTs, which have higher risk of recurrence[22,23] and demonstrated a worse prognosis in our study. Current guidelines include recommendation of 36 months of adjuvant imatinib for adult patients with CD117-positive GISTs at high risk of relapse,[31,34,37] based on the results of Scandinavian-German SSGXVIII/AIO trial.[22,23]

To summarize, our analysis comprising the largest group of GIST patients treated with neoadjuvant imatinib in routine practice indicates excellent long-term results of combined therapy in locally advanced GISTs. Postoperative imatinib therapy should be used routinely in patients considered for neoadjuvant therapy, because it is highly unlikely that such tumors belong to very low/low-risk GIST. Present indications for preoperative imatinib treatment in GISTs include locally advanced tumor, not *amenable* to surgery without *mutilating operation* (e.g., abdominoperineal resection, pelvic evisceration), when negative resection margins around the organ of origin are difficult to obtain, and when function-sparing resection and minimizing the extent of surgery can be possible after tumor shrinkage (e.g., wedge resection instead of total gastrectomy with splenectomy, local excision instead of pancreatoduodenectomy).

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