Surgical treatment of locally advanced, non-metastatic, gastrointestinal stromal tumours after treatment with imatinib

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Abstract

Aims: Patients with locally advanced gastrointestinal stromal tumours (GISTs) have a high risk of tumour perforation, incomplete tumour resections and often require multivisceral resections. Long-term disease-free and overall survival is usually impaired in this group of patients. Induction therapy with imatinib followed by surgery seems to be beneficial in terms of improved surgical results and long-term outcome. We report on a large cohort of locally advanced GIST patients who have been treated in four centres in the Netherlands specialized in the treatment of sarcomas.

Methods: Between August 2001 and June 2011, 57 patients underwent surgery for locally advanced GISTs after imatinib treatment. Data of all patients were retrospectively collected. Endpoints were progression-free and overall survival.

Results: The patients underwent surgery after a median of 8 (range 1–55) months of imatinib treatment. Median tumour size before treatment was 12.2 (range 5.2–30) cm and reduced to 6.2 (range 1–20) cm before surgery. No tumour perforation occurred and a surgical complete (R0) resection was achieved in 48 (84%) patients. Five-year PFS and OS were 77% and 88%. Eight patients had recurrent/metastatic disease.

Conclusions: Imatinib in locally advanced GIST is feasible and enables a high complete resection rate without tumour rupture. The combination of imatinib and surgery in patients with locally advanced GIST seems to improve PFS and OS.

Keywords: Gastrointestinal stromal tumour; Surgery; Imatinib

Introduction

Gastrointestinal stromal tumours (GISTs) are the most common soft tissue tumours of the gastrointestinal tract, which arise from the interstitial cells of Cajal. The estimated prevalence is 1–2 per 100 000 persons. Most GISTs express KIT, a tyrosine kinase receptor, which can be detected by immunohistochemistry using the CD117 antibody. Over 80% of GISTs have an activating mutation in the KIT or, less often, the PDGFRA gene.

Historically, treatment for locally advanced GISTs has relied on surgery as the first-line intervention, as response rates to conventional chemotherapy were less than 10%. Approximately 70–85% of GISTs are primary resectable at first presentation depending on anatomic site and/or tumour size. A high mitotic activity, large tumour size, incomplete surgical resection and tumour perforation have been identified as negative prognostic factors for relapse and survival.
In 2001, imatinib mesylate, a small molecular receptor tyrosine kinase inhibitor, was found to inhibit mutated KIT or PDGFA receptor tyrosine kinases.\textsuperscript{12,13} Imatinib has been demonstrated to achieve partial response or stable disease in nearly 80% of patients with advanced GIST.\textsuperscript{12–14} Treatment with imatinib is generally well-tolerated with mild side effects and is considered first-line treatment in metastasized GIST patients.\textsuperscript{14} Nevertheless, progression of disease occurs at a median time of 2 years from start of treatment through acquisition of additional activating c-KIT or PDGFA mutations in tumour clones rendering them imatinib refractory.\textsuperscript{15,16}

Before the era of imatinib, surgical resection of locally advanced GISTs larger than 5 cm resulted in a median overall survival (OS) of approximately 30 months and a recurrence rate of up to 60% within 2 years.\textsuperscript{7–9} Because imatinib induces downsizing of large tumours, it could potentially reduce the risk of tumour rupture during surgery and provide an opportunity for a surgical complete and less morbid (i.e. organ-sparing) resection.\textsuperscript{17} This could lead to an improved disease-free and overall survival in patients with locally advanced GISTs. Reports on surgical resection following imatinib treatment in patients with locally advanced GIST are limited and usually consist of small retrospective patient series.\textsuperscript{17–22} Most of these studies also included patients with both locally advanced and metastatic disease. The present study is the first to retrospectively evaluate the long-term outcome in a large group of patients who underwent surgery for locally advanced, non-metastatic, GIST after treatment with imatinib.

### Methods

#### Patients and preoperative treatment

We reviewed all patients with a locally advanced GIST who received imatinib before surgery was undertaken at four Dutch institutions (The Netherlands Cancer Institute, Amsterdam; Leiden University Medical Centre, Leiden; Radboud University Nijmegen Medical Centre, Nijmegen; Erasmus Medical Centre, Daniel Den Hoed Cancer Centre, Rotterdam). These patients were evaluated in a multidisciplinary sarcoma board at each centre before start of treatment. All tumours were considered too large (>5 cm) and/or ill-located for surgery by the sarcoma board. Therefore, imatinib was started in an attempt to downsize the tumour and prevent peroperative tumour rupture with a possibly less mutilating resection. Before start of imatinib a baseline CT was performed, and all patients were clinically and radiographically re-evaluated until surgery. Patients were classified as having a complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) on the use of imatinib, based on serial imaging and scored according to Response Evaluation Criteria in Solid Tumours (RECIST).\textsuperscript{23} The decision when to perform surgery was tailor-made for each patient at the time the multidisciplinary sarcoma board thought of a maximum therapeutic response.

We collected patient- and treatment-specific data from prospectively kept sarcoma databases, medical records databases and patient charts at every institution. Data included initial symptoms, date of diagnosis, histopathological analyses, duration and dose of imatinib, complications on imatinib, best response to imatinib, date of surgery, type of surgical resection and (postoperative) complications, adjuvant imatinib treatment, date of recurrent/metastatic disease after surgery, last follow-up and disease status at last follow-up, and if applicable, date of death.

#### Surgery and postoperative treatment

All resections were classified as R0 (macroscopically complete resection with negative microscopic margins), R1 (macroscopically complete resection with positive microscopic margins) or R2 (macroscopically incomplete resection). Recurrent disease appearing after surgery in the region of the previously located tumour is called ‘recurrence’, and disease that had spread to distant sites, such as the liver, is called ‘metastasis’. Imatinib treatment was restarted depending on completeness of resection and preference of the treating physicians. Status of disease at last follow-up was determined using the most recent physical and radiographical evaluation. If a patient had deceased, date of death and status of disease at death were recorded. The data of each patient was updated until July 2011.

#### Endpoints and statistics

Progression-free survival (PFS) was defined as the time from date of surgery to the date of clinical evidence of recurrent or metastatic disease, date of last follow-up or death from any cause, whatever occurred first. OS was defined as the time from surgery to date of last follow-up or patient death. PFS and OS were estimated using the Kaplan–Meier method. Statistical analysis was performed using SPSS statistical software, version 16.0.

#### Results

##### Patients and preoperative imatinib treatment

A total of 57 patients (35 men and 22 women) were eligible for evaluation. The median age was 61 (range 29–82) years at the time of surgery after treatment with imatinib. Details on tumour location and imatinib treatment are summarized in Table 1. All GISTs were confirmed by experienced sarcoma pathologists at each centre and were characterized by a positive c-KIT expression. Other tumour markers were not commonly assessed. Mutation status was available in 30 patients: KIT exon 11 (n = 18), KIT exon 9 (n = 1), KIT exon 12 mutation (n = 1), KIT exon 18 mutation (n = 1), KIT exon 9 and 17 mutation (n = 1),
wildtype \((n = 4)\), no KIT exon 9 or 11 mutation \((n = 3)\). In the remaining 27 patients, the mutation status was not determined because it was not routinely performed in the past or analysis was not possible due to technical difficulties. Median tumour size was 12.2 (range 5.2–30) cm before start of imatinib. Treatment with imatinib 400 mg daily was the first choice of treatment in all patients. The primary tumour size, possible invasion of surrounding organs on CT-imaging and technical difficult surgical procedures (i.e. ill-location), surgery was not the first choice in treatment. Two patients experienced gastrointestinal complications and imatinib was lowered to 300 mg daily before surgery. Two patients with a PR had to stop using imatinib after 1 and 4 months because of severe toxidermic complications and progressive (pre-existent) renal failure. Surgery followed within two weeks after stopping imatinib. Two patients shortly interrupted imatinib because of gastrointestinal complications and oedema, after a short stop imatinib was continued at 800 mg daily dose because of disease progression. Three patients experienced disease progression from start of imatinib and switched to 800 mg daily. Two patients experienced a PR and one patient PD after starting the higher dose and surgery followed after 2, 2, and 4 months, respectively. No patient was switched to second-line therapy. The tumour size after a median of 8 (range 1–55) months of treatment with imatinib was 6.2 (range 1–20) cm. One patient had a CR, 46 patients had a PR, 7 patients had SD and 3 patients had PD at the time of surgery. One patient experienced an ongoing (partial) response before disease stabilization at 51 months. Surgery followed at 55 months.

**Surgical outcome and postoperative treatment**

All patients underwent elective surgery and the procedures are listed in Table 2. In 6 patients no viable tumour could be demonstrated at final pathology. An R0 resection was achieved in 48 patients and an R1 resection in 8 patients. In 1 patient, resection of the tumour was not considered feasible during surgery because of extensive tumour invasion in liver, spleen, pancreas and duodenum. Despite tumor shrinkage 19 patients were surgically treated with an en-bloc multivisceral resection. In the other patients, a less mutilating procedure was performed. One patient underwent a partial resection of the anterior wall of the rectum because the tumour was located between the prostate and rectum. The tumour was removed without performing a low anterior resection. Thirteen patients experienced at least one surgical complication, with a total of 20 complications (Table 3). Reoperations for complications were required in four patients; postoperative bleeding (one), bowel perforation (one), and anastomotic leakage of large bowel (two). No postoperative mortality was observed within 30 days of surgery. One patient with a bowel perforation died 44 days after surgery. In 33 patients, imatinib was continued following surgery for 1, 2 years or lifelong after evaluation in the sarcoma board.

**Progression-free and overall survival**

Complete follow-up data were available for 55 patients. Two 2 patients were lost to follow-up. Median PFS measured from time of surgery has not been reached, and one-, three- and five-year PFS have been estimated at 96%, 87% and 77%. Eight patients experienced recurrent/metastatic disease; 3 patients during adjuvant imatinib treatment and 5 patients without adjuvant imatinib treatment. These five patients were treated with imatinib at the time of diagnosis of recurrent/metastatic disease. PFS based on adjuvant imatinib treatment is shown in Fig. 1.
Although a trend to a higher PFS in the adjuvant imatinib group was shown, it was not significantly different \((p = 0.11)\). Seven patients developed distant metastasis: peritoneal \((n = 4)\), liver \((n = 1)\), peritoneal and liver \((n = 1)\) and abdominal wall \((n = 1)\). One patient experienced a local recurrence after an intersphincteric rectum amputation. Surgical procedures were performed in three patients because of metastatic lesions. One patient underwent resection of several metastatic peritoneal lesions and a splenectomy 11 months after initial surgery, and has no evidence of disease 23 months after initial surgery. One patient underwent a partial liver resection 26 months after resection of the primary tumour. Because of re-occurrence metastases, radiofrequency ablation of liver metastases and resection of 2 peritoneal metastatic lesions combined with a partial small bowel resection was performed after 51 months. This patient died of disease 59 months after initial surgical treatment. Finally, one patient underwent resection of abdominal wall metastases and resection of 2 peritoneal lesions 9 months after initial surgery. This patient is alive without evidence of disease.

At recent follow-up, 44 patients had no evidence of disease, 4 patients were alive with disease, 4 patients had died of disease and 3 patients died because of other reasons. Median OS has not been reached, one-, three-, and five-year OS have been estimated at 100%, 96% and 88% (Fig. 2). Four patients died of GIST. No correlation between clinical, pathological, and treatment variables with prognosis could be demonstrated due to small sample size.

Discussion

This study is the largest study to date to report long-term outcome of patients who underwent surgical resection of locally advanced, non-metastatic GIST after imatinib therapy. Larger studies are available reporting the results of both locally advanced and metastatic GIST together as one group with or without surgery after imatinib therapy, which makes it difficult to compare with the results of this study.\(^{15,20}\) Several reports differentiate between locally advanced and metastatic GIST, but are usually comprised of small patient series with a limited follow-up (Table 4). The present series demonstrates a high 5-year PFS and OS of 77% and 88% in a multicentre collected group of patients with locally advanced GIST.

Surgery remains the only possible curative treatment for GIST. Approximately 70–85% of patients with localized GISTs can undergo a complete resection at first presentation.\(^7,24\) A surgical complete resection is the most important prognostic factor for patients with locally advanced, non-metastatic GIST. Furthermore, large tumours carry an increased risk of tumour rupture, which has a detrimental effect on disease-free and overall survival. Tumour rupture reduced the median survival to approximately 17 months.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Follow-up (median/months)</th>
<th>Survival and disease status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andtbacka et al., 2006(^{20})</td>
<td>11</td>
<td>19.5</td>
<td>All alive at last follow-up; 10 NED, 1 RD</td>
</tr>
<tr>
<td>Raut et al., 2006(^{21})</td>
<td>9</td>
<td>14.6(^a)</td>
<td>95% 1- year survival SD, 86% 1-year survival LP, 0% 1-year survival GP(^a)</td>
</tr>
<tr>
<td>Mearadij et al., 2008(^{19})</td>
<td>9</td>
<td>40</td>
<td>All alive at last FU; 7 NED, 2 AWD</td>
</tr>
<tr>
<td>Eisenberg et al., 2009(^{17})</td>
<td>30</td>
<td>36</td>
<td>83% 2-year PFS, 93% 2-year OS</td>
</tr>
<tr>
<td>Fiore et al., 2009(^{18})</td>
<td>15</td>
<td>34</td>
<td>14 alive at last FU; 12 NED, 2 RD, 1 DD</td>
</tr>
<tr>
<td>Blesius et al., 2011(^{22})</td>
<td>9</td>
<td>53.5</td>
<td>67% 3-year PFS, 89% 3-year OS</td>
</tr>
<tr>
<td>Present study</td>
<td>57</td>
<td>43</td>
<td>47 alive at last FU, 4 AWD, 3 DD</td>
</tr>
</tbody>
</table>

NED, no evidence of disease; RD, recurrent disease; AWD, alive with disease; DD, died of disease.

\(^a\) Patients were divided in three categories: stable disease (SD), limited progression (LP), and generalized progression (GP).
comparable to the median survival of 21 months after an incomplete resection in the pre-imatinib era as reported by Ng et al.9 Recently, Hohenberger et al. reported that nearly all patients develop abdominal metastases after rupture of GIST.11 Therefore, if a GIST is large and the risk of tumour rupture is considered high, imatinib treatment should be started to increase the chance of an R0 resection and decrease the potential risk of tumour perforation during surgery.

The discovery of gain-of-function KIT mutations in GIST by Hirota et al. and the introduction of imatinib, the small-molecular targeted therapy, revolutionized the management of GIST.4,12 Currently, imatinib is approved worldwide as the first-line treatment of metastatic GIST. Toxicity and primary resistance to imatinib are the main limitations of this drug.13,25 Secondary resistance, defined as progressive disease at least 3 months after initiation of imatinib, usually occurs at a median time of 2 years after start of treatment.13 Timing of resection is important if imatinib is used as induction therapy in locally advanced tumours. If surgery is performed beyond the window of therapeutic response, resistance or metastases might develop.15 In the present study, the median interval between start of imatinib and surgery was 8 months, and no patient switched to second-line therapy because of disease progression. This might indicate that all tumours reached a plateau in their response to imatinib. A favourable outcome for responding patients undergoing surgery following imatinib has already been suggested in metastasized patients.19–21 Although this has not been confirmed in a randomized trial.

In this study, tumour response on imatinib has been assessed by a combination of physical and radiological examination. A partial response on CT scan according to RECIST requires at least 6 months of imatinib therapy.15 Using size-based response criteria such as RECIST might underestimate the response to imatinib as suggested by clinical experience in the last few years.26,27 Changes in tumour nodules and vascularization should be combined with tumour density and smaller changes in size to evaluate potential responses by CT faster. A positron emission tomography (PET) using 18F-fluorodeoxyglucose (18FDG) may predict responses to therapy better on short-term follow-up. It is instrumental when CT findings are inconsistent with clinical findings.26,28,29 Response measurement using these 18FDG-PET scan criteria was not always possible because of the retrospective nature of this study. Most patients were diagnosed with GIST in other hospitals and an 18FDG-PET scan was not always available.

Given the anti-tumour activity of imatinib in the metastatic setting, with response rates of over 50%, imatinib is increasingly used. In patients with locally advanced GISTs, i.e. when resection is judged impossible or at the cost of considerable morbidity, it is now commonly used as induction therapy. Randomized controlled studies are hard to conduct for multiple reasons and the only prospective multicentric neo-adjuvant imatinib trial was the RTOG study.17 A better insight needs to be obtained by retrospective series. In the present study, adequate clinical downsizing of the tumour with preoperative imatinib therapy was demonstrated in 52 patients who underwent an R0 resection without tumour perforation. This reflects the main advantage of imatinib as induction therapy in patients with locally advanced GIST. A less extensive resection rate was not clearly demonstrated in this study as 19 patients underwent multivisceral resections. However, most multivisceral resections (n = 14) were performed in the early treated patients and after 2007 less extensive resections have become more common. This bias is probably caused by increased knowledge of the potential benefits of imatinib and the tendency of locally advanced GIST not to invade surrounding organs.

At a median postoperative follow-up time of 40 months, the 5-year estimated PFS was 77% measured from surgery. This seems an improvement compared to historical data, since patients with tumours larger than 10 cm experienced a disease-specific 5-year survival of only 20% after resection in recent literature.7,8 However, this comparison is biased because 33 patients received adjuvant treatment with imatinib. Median PFS for patients treated with adjuvant imatinib has not been reached and for patients who received no adjuvant treatment it was 49 (range 9–56) months. In the phase III trial, patients with GISTs larger than 3 cm underwent surgical resection and received adjuvant imatinib or placebo for 1 year.25 Significantly fewer recurrences were noted in patients who received imatinib for 1 year after complete resection compared to patients receiving placebo. Median recurrence-free survival was not reached for tumours between 6 and 10 cm, and median recurrence-free survival for tumours 10 cm or greater was approximately 35 months in the imatinib group. Recently, Joensuu et al. reported that administration of imatinib for 36 months after surgery improves recurrence-free and overall survival compared to 12 months in patients with a high estimated risk of recurrence.30 Although these results have to be published, adjuvant treatment with imatinib is now considered standard treatment in the referral hospitals of this study group.

Median OS after surgical resection of GISTs larger than 5 cm is reported to be approximately 27–32 months.7,9 The OS in the present study is substantially higher with 83% of patients alive at 5 years, and median OS not reached after 49 months. This might suggest that imatinib therapy followed by surgical resection enables adequate surgical resections with a low chance on tumour perforation and might prolong OS. Once again, firm conclusions are hard to draw as the current median OS of patients with metastatic disease treated with imatinib and/or sunitinib has meanwhile dramatically improved as well.

Conclusion

Evaluation of patients with a locally advanced, non-metastatic GIST in a multidisciplinary tumour board in high-volume GIST centres has proven to be successful. It
supplies the best strategy for treatment and prevention of disease progression. Imatinib as induction therapy is considered a useful tool in patients with locally advanced GIST. This results in a decrease of tumour size in most patients, and thereby increases the chances of a surgical complete resection without tumour rupture. Combining imatinib and surgery in patients with locally advanced GIST seems to improve PFS and OS compared to available historical reported series.

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Conflict of interest

Hereby, all authors declare to have no conflicts of interest as stated and signed by all authors in the “Author Form”.

References