Available online at www.sciencedirect.com
SciVerse ScienceDirect
EJSO 39 (2013) 150–155
EJSO the Journal of Cancer Surgery
www.ejso.com

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

R. Tielen [a,*], C. Verhoef [c], F. van Coevorden [e], H. Gelderblom [g], S. Sleijfer [d], H.H. Hartgrink [f], J.J. Bonenkamp [a], W.T.A. van der Graaf [b], J.H.W. de Wilt [a]

[a] Department of Surgical Oncology, Radboud University Nijmegen Medical Centre, Geert Grooteplein 10, 6525 GA Nijmegen, The Netherlands
[b] Department of Medical Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[c] Department of Surgical Oncology, Erasmus Medical Centre, Daniel Den Hoed Cancer Centre, Rotterdam, The Netherlands
[d] Department of Medical Oncology, Erasmus Medical Centre, Daniel Den Hoed Cancer Centre, Rotterdam, The Netherlands
[e] Department of Surgical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[f] Department of Surgical Oncology, Leiden University Medical Centre, The Netherlands
[g] Department of Medical Oncology, Leiden University Medical Centre, The Netherlands

Accepted 26 September 2012
Available online 16 October 2012

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.[1] The estimated prevalence is 1–2 per 100 000 persons.[2,3] Most GISTs express KIT, a tyrosine kinase receptor, which can be detected by immunohistochemistry using the CD117 antibody.[1] Over 80% of GISTs have an activating mutation in the KIT or, less often, the PDGFRA gene.[4–6]

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%.[7,8] 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.[1,3,9–11]

* Corresponding author. Tel.: +31 24 361 3808; fax: +31 24 354 0501.
E-mail address: r.tielen@chir.umcn.nl (R. Tielen).

0748-7983/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejso.2012.09.004

In 2001, imatinib mesylate, a small molecular receptor tyrosine kinase inhibitor, was found to inhibit mutated KIT or PDGFA receptor tyrosine kinases.[12,13] Imatinib has been demonstrated to achieve partial response or stable disease in nearly 80% of patients with advanced GIST.[12–14] Treatment with imatinib is generally well-tolerated with mild side effects and is considered first-line treatment in metastasized GIST patients.[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.[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.[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.[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.[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).[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 ($n = 1$),