

Duration of adjuvant treatment following radical resection of metastases from gastrointestinal stromal tumours

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Received September 16, 2011; Accepted December 9, 2011

DOI: 10.3892/ol.2011.537

Abstract. Large-scale studies have demonstrated that continuative treatment in advanced and adjuvant settings results in a gain-of-survival. However, the discontinuation, and the duration of treatment in disease-free patients who have undergone radical surgical resection of metastases from gastrointestinal stromal tumours (GISTs) have yet to be evaluated. We retrospectively reviewed 40 patients with advanced and recurrent GIST, included in our GIST database, focusing on patients (5 males and 2 females; median age 56 years) who continued medical treatment following radical surgical resection of metastatic lesions. Seven out of 40 patients underwent surgery and continued medical treatment following radical surgical resection of metastatic lesions. The duration of adjuvant therapy was 3, 12, 16, 24, 35, 37 and 52 months, respectively, with a median of 26 months. No patients discontinued therapy and all were disease-free at the final CT-scan evaluation. Considering that the discontinuation of imatinib in responding patients with advanced GIST (even in complete remission) results in a rapid high risk of progression, and a short adjuvant therapy results in a shorter disease-free and overall survival in high-risk GIST patients, it is also likely that treatment should not be discontinued in this setting. However, large-scale studies are required to better assess the optimal duration of treatment,

particularly after 5 years, by focusing on the identification of predictive factors for the selection of patients who may benefit from a prolonged or lifelong imatinib treatment.

Introduction

In the last ten years the introduction of imatinib, a small tyrosine-kinase inhibitor (TKI), selective for KIT and platelet-derived growth factor receptor (PDGFRA), has markedly modified the natural history of gastrointestinal stromal tumours (GISTs). Imatinib is the worldwide standard treatment for non-operable/advanced/recurrent disease and, more recently, for patients with a substantial risk of relapse (1-3).

The discontinuation of treatment in advanced disease, even in patients who have achieved a radiological complete remission, is not recommended unless severe toxicity occurs, since imatinib interruption results in a high risk of rapid progression (4-6).

In the adjuvant setting, the current recommendation is the use of imatinib for 1 year, although 3 years of administration compared to 1 year recently led to an improvement in relapse-free and overall survival in GIST patients with a high estimated risk of recurrence following surgery (3).

Whereas large-scale studies have shown that continuative treatment in advanced and adjuvant settings results in a gain-of-survival, the discontinuation, and thus the duration of treatment, in disease-free patients who underwent radical surgical resection of metastatic GISTs has yet to be investigated.

Currently, ESMO clinical practice guidelines recommend that patients with advanced/recurrent GIST responding to imatinib should continue treatment indefinitely, even in the postoperative setting, with an evidence level of II (7).

The present study reports on the long-term outcome of patients from S.Orsola-Malpighi Hospital (Italy) who continued medical treatment following radical surgical resection of advanced/metastatic GISTs.

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Key words: gastrointestinal stromal tumours, KIT, platelet-derived growth factor receptor, imatinib, adjuvant therapy, discontinuation, tyrosine-kinase inhibitors

Materials and methods

Patients. We retrospectively reviewed 40 patients with advanced and recurrent GIST, included in our GIST database, focusing on patients who continued medical treatment following radical surgical resection of metastatic lesions. Of the 40 patients with advanced or recurrent GIST, 7 patients received surgery and continued medical treatment following radical surgical resection of metastatic lesions. Patient characteristics are shown in Table I. The group comprised 5 (71%) males and 2 (29%) females. Age had a unimodal distribution, with a median of 56 years (range, 30-68). The primary tumour site was the stomach in 6 patients (86%) and small intestine in 1 patient (14%).

Primary tumour risk stratification was defined according to the NIH and Miettinen classifications (8,9). According to Miettinen's classification, risk stratification included the following: 5 patients (71%) had a high-risk tumour, 1 patient (14.5%) had an intermediate-risk tumour and 1 patient (14.5%) had a low-risk tumour. The sites of metastasis were the liver in 4 patients (57.1%), peritoneum in 1 patient (14.3%), liver and peritoneum in 1 patient (14.3%) and liver and lymph nodes in 1 patient (14.3%).

Four patients had advanced GIST at the time of diagnosis, whereas 3 patients relapsed 10, 35 and 39 months, respectively, following primary tumour resection.

Methods. Mutational analysis of KIT and PDGFRA was performed on genomic DNA extracted from paraffin-embedded tumour tissue by KIT Qiagen (QiAamp DNA FFPE Tissue Kit) using a combination of polymerase chain reaction (PCR) amplification and automated sequencing. The mutational analysis only on primary GIST tumours was performed in 6 out of 7 patients: 4 patients harboured a KIT exon 11 mutation, 1 patient harboured a PDGFRA exon 18 mutation and 1 patient had a wild-type (WT) GIST. Among these patients, the mutational analysis on metastases was performed only in 2 patients and exhibited the same mutational status of the primary GIST, whereas in 2 patients mutational analysis was not achievable due to huge necrosis following medical treatment, and in the other 2 patients the biological samples were not available. In the only remaining patient (patient 1) where the mutational analysis was not carried out on the primary GIST tumour, it was performed on the metastatic tissue and the result was a KIT exon 11 mutation associated to a secondary exon 17 mutation (Table II).

Results

Findings of CT-PET scan and CT scan. Seven patients underwent radical surgical resection of metastases from GIST. Of 4 patients with advanced GIST at the time of diagnosis, 3 were treated with primary tumour excision followed by imatinib (400 mg daily) as first-line treatment for the metastases, while the remaining patient underwent radical primary tumour and metastases excision up-front. Of 3 patients with recurrent GIST, 2 were treated with imatinib (400 mg daily) as first-line treatment, while the remaining patient underwent surgical excision of the metastatic lesions up-front. The duration of first-line treatment with imatinib (400 mg daily) was 16, 19

Table I. Patient characteristics.

Number of patients	Total (n=7)
Gender	
Male	5 (71%)
Female	2 (29%)
Age (years)	
Median	56
Range	30-68
Primary tumour site	
Stomach	6 (86%)
Small intestine	1 (14%)
Risk	
Low	1 (14.5%)
Intermediate	1 (14.5%)
High	5 (71%)
Stage at time of diagnosis	
Localised	3 (37.5%)
Advanced	4 (62.5%)
Sites of metastasis	
Liver	4 (57.1%)
Peritoneum	1 (14.3%)
Liver and peritoneum	1 (14.3%)
Liver and lymph nodes	1 (14.3%)

and 34 months in 3 advanced GIST patients, and 16 and 11 months in 2 recurrent GIST patients. Therefore, 5 patients received imatinib treatment at a dose of 400 mg daily prior to the surgical removal of metastases, and 2 patients underwent surgery up-front without medical treatment. Of those 5 patients, 3 had an early complete response at CT-PET scan performed 7 days following start of therapy. Four patients underwent surgery at best radiological response assessed by CT scan, whereas only 1 patient (patient 1) received a second-line treatment with imatinib (800 mg daily), due to disease progression, for a duration of 11 months, and then underwent surgery at best radiological response.

Following surgery, all 7 patients continued the same medical treatment received prior to surgical procedures without discontinuation for 3, 12, 16, 24, 35, 37 and 52 months, respectively, with a median of 26 months. The patients were disease-free at the final CT scan evaluation.

Pathological tumour response. Pathological tumour response was assessed in 4 out of 5 patients who received medical treatment prior to surgical removal of metastases of whom 3 had a high pathological response (tumour necrosis >90%) and 1 patient had a moderate pathological response (tumour necrosis: 50-90%) according to criteria determined by Antonescu *et al* (10).

Discussion

Although the introduction of imatinib has changed the natural history of GIST, treatment duration in various settings of disease

Table II. KIT and PDGFRA mutational analysis.

Patient	Primary tumour	Metastases
1	NP ^a	c.1674_1695del KIT exon 11 (p.Lys558_Gly565del) c. T>A 2466 KIT exon 17 (p.Asn822 Lys)
2	PDGFRA exon 18 c.2523_2531del (p.Asp842_Met844del)	NP ^b
3	KIT exon 11 c.1727 T>C (p.Leu576Pro)	NP ^b
4	KIT exon 11 c.1669_1674 (p.Trp557_Lys558)	KIT exon 11 c.1669_1674 (p.Trp557_Lys558)
5	KIT exon 11 .1669_1647del (p.Trp557_Lys558)	NP ^a
6	Wild-type	Wild-type
7	KIT exon 11 delWK557-558	NP ^a

^aNP, not performed as tumour samples were not appropriate due to huge necrosis following medical treatment. ^bNP, not performed as tumour samples were not available. PDGFRA, platelet-derived growth factor receptor.

remain to be investigated. The imatinib-dependent selection of resistant tumour clones harbouring novel mutations, and the potential decline of quality of life due to a daily chronic therapy have questioned the duration of therapy, in advanced disease and, more recently, in radically resected limited disease.

In advanced disease the discontinuation of imatinib has been shown to result in a high risk of disease progression in responder patients with advanced GIST (4-6). In particular, imatinib interruption following 3 years of treatment led to a rapid progression, with a median progression-free survival of only 9 months (4). However, the difference in progression-free and overall survival between patients in the interruption group who resumed imatinib at the time of progression and patients in the continuation group was not statistically significant, even if imatinib re-introduction re-established tumour control in the majority of, but not all, patients (4,5).

The same finding has also been reported in patients with chronic myeloid leukaemia (CML) in complete molecular remission for at least 2 years: 61% of patients who discontinued treatment had a molecular relapse following a median follow-up of 21 months (11). Therefore, these data, confirmed in various tyrosine kinase-driven malignancies, including GIST and CML, suggest that imatinib is unable to eradicate microscopic residual tumour clones in patients who achieved a complete remission. Thus, imatinib alone is unable to cure patients with advanced GIST, even in radiological complete remission; therefore, in this setting medical treatment should be prolonged until progression or intolerance (7).

Furthermore, a subset of patients with advanced GIST survived over 9 years with continuous imatinib therapy, without unexpected long-term toxicities (12). Among 147 patients with advanced GIST initially enrolled in the first large trial B2222, 26 patients (17.7%) remained on continuous imatinib from study entry (12). Low tumour bulk at baseline was identified as a predictive factor for longer time to progression and improved overall survival (12).

Moving to the adjuvant setting, the recent results from the SSGXVIII/AIO trial have demonstrated that 3 years of imatinib administration as adjuvant treatment for GIST patients at a high risk of recurrence following surgery led to an improvement in relapse-free and overall survival compared to 1 year of treatment (3). According to these data, patients with minimal residual disease may also benefit from a prolonged treatment with imatinib, suggesting that patients with a substantial risk of GIST are eligible for long-term therapy.

By contrast, the discontinuation of treatment in disease-free patients following radical surgical resection of advanced/metastatic GIST has not yet been investigated. Thus, the duration of treatment in this specific setting remains to be elucidated.

It is now accepted that surgery for residual disease upon best clinical response is associated with survival benefits in certain retrospective studies (13-19). In particular, Mussi and colleagues recently reported a significant improvement in disease-specific survival in patients who underwent surgical resection of metastatic or recurrent GIST upon best response in comparison with historical controls treated with imatinib alone (13). In this study, the 7 patients who underwent surgical resection upon best response continued imatinib following surgery, with a 2-year progression-free survival rate of 64.4%, suggesting that treatment interruption should be avoided even when lesions have been surgically excised (13).

We reported the long-term outcome of 7 patients from S.Orsola-Malpighi Hospital who continued medical treatment following radical surgical resection of advanced/metastatic GIST. The mean treatment duration was 26 months without discontinuation and all patients remained disease-free at the final CT evaluation. Three patients did not have evidence of disease after more than 3 years.

Despite the small case series, our report raises certain issues designed to open the debate on this topic. Considering that the discontinuation of imatinib in responder patients with advanced GIST, even in complete remission, results in

a rapid high risk of progression, and a brief adjuvant therapy results in a shorter disease-free and overall survival in high-risk GIST patients, it is also likely that treatment should not be discontinued in this setting. Adjuvant imatinib treatment in GIST patients following surgical removal of metastases is well consolidated in clinical practice although no prospective trials are available. By contrast, the role of adjuvant chemotherapy in other diseases, such as colorectal cancer, following complete resection of metastases remains under debate and its use is still restricted in clinical practice due to the lack of consistent clinical trials supporting its benefit with regards to progression-free and overall survival (20,21).

However, the optimal duration of treatment, particularly in patients with no evidence of disease after 5 or more years of therapy is likely to remain controversial for as long as the optimal duration of adjuvant therapy remains undefined.

Furthermore, novel risk stratification systems are essential for this subset of patients to select those patients that may benefit from treatment discontinuation. New nomograms for the prediction of recurrence-free survival following surgery for GIST-presenting risk of recurrence as a continuous scale have recently been proposed (22). However, the incorporation of other biological variables may increase the precision of these systems, particularly if applied to a complex subset of patients with an intrinsic high risk of recurrence, since they have already relapsed.

Three patients in our small series had a high pathological tumour response, and 1 had a moderate pathological tumour response to treatment received prior to the surgical removal of metastases. This finding suggests that pathological tumour response to pre-operative therapies exhibits a predictive value of recurrence-free survival following the radical surgery of metastases from GIST. In addition, the data on molecular analysis should be considered. In our series, 6 out of 7 patients have KIT/PDGFR α -sensitive mutations to imatinib in primary GIST tumours. In particular, the only patient who was resistant to imatinib (400 mg daily) harboured a KIT exon 11 mutation associated to a KIT exon 17 secondary mutation on the metastases, and experienced a tumour response following imatinib dose escalation to 800 mg/day. Only 1 patient underwent radical primary tumour and metastases excision up-front and has a WT GIST that, as far as is known, may be less sensitive to imatinib. However, since the patient was 29 years of age and exhibited a high risk of recurrence, imatinib treatment was commenced.

The risk of selecting novel tumour clones harbouring resistant mutations during a prolonged treatment may be higher in patients who had metastatic disease, even if it has not been demonstrated that long-term exposure to TK inhibitors affects the development of secondary resistance mechanisms.

Finally, the subjective compliance with a chronic treatment may interfere with the assessment of optimal treatment duration in each clinical setting. It is noteworthy that in the SSGXVIII/AIO trial, the proportion of patients who discontinued imatinib during the assigned treatment period not due to disease recurrence was 25.8% in the 36-month group in comparison to 12.6% in the 12-month group (3).

In conclusion, the optimal duration of treatment in disease-free patients undergoing radical surgical resection of metastatic GIST has not yet been established. Highlighting

recent evidence on imatinib discontinuation in complete remission advanced GIST patients, it is probable that treatment interruption should also be avoided following radical surgical excision of metastatic lesions. However, the duration of treatment in this particular clinical setting remains to be investigated and the decision to suspend treatment should be taken with the individual patient, particularly after 5 years.

Large-scale retrospective studies are required to evaluate the outcome of disease-free patients undergoing radical surgical resection of metastatic GIST following treatment discontinuation. Furthermore, novel molecular biomarkers must be identified to select those patients with a higher risk of relapse, who may benefit from prolonged or lifelong imatinib treatment.

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