



CASE REPORT

Excision of a Large Gastrointestinal Stromal Tumour Following 16 Months of Neoadjuvant Therapy with Imatinib (Case Report)

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ABSTRACT

Introduction: Although the standard treatment for stromal tumours is surgery, in locally advanced forms, it is often necessary to achieve tumour downstaging to improve surgical outcomes. Neoadjuvant treatment in gastrointestinal stromal tumours (GISTs) with tyrosine kinase inhibitors, including imatinib, has been

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shown to be effective in several studies, but the duration of this treatment is still a subject of debate.

Case report: We report a case of a large GIST of the stomach in a 51-year-old patient with atypical presentation that was initially unresectable. Neoadjuvant treatment with imatinib for 16 months resulted in a good response, allowing secondary surgical excision.

Conclusion: Imatinib in neoadjuvant therapy should be continued as long as there is a good response and tolerance to the medication to obtain tumour downsizing compatible with carcinologic excision.

Keywords: GIST; Imatinib; Neoadjuvant therapy; Surgery

Abbreviations

GIST	Gastrointestinal stromal tumour
CT	Computed tomography
CD	Cluster of differentiation
KIT	Tyrosine protein kinase cKIT
PDGFRA	Platelet-derived growth factor receptor α
PET	Positron emission tomography
EORTC	European Organisation for Research and Treatment of Cancer
RTOG	Radiation Therapy Oncology Group
ESMO	European Society for Medical Oncology

Key Summary Points

The duration of neoadjuvant treatment of GISTs with imatinib remains a subject of debate

Some authors recommend not to exceed 12 months. But there is no scientific basis for this delay

Through this clinical case, the authors report a good tolerance and a good tumour response after 16 months of neoadjuvant treatment with imatinib, allowing the excision of a large gastric stromal tumour, and discuss the criteria to determine the duration of the neoadjuvant treatment

The authors suggest, in the context of neoadjuvant therapy, to continue treatment as long as there is good tumour response and tolerance allowing carcinologic excision

INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are tumours that are derived from Cajal cells or their precursors. These are the most frequent mesenchymal tumours of the digestive tract [1]. They represent 0.1–3% of all gastrointestinal tumours, and gastric localisation is the most frequent [2]. Although the standard of care is surgery, the prognosis of these tumours has been improved by tyrosine kinase inhibitors, which have increased overall and disease-free survival rates [3–7]. GISTs may sometimes be diagnosed at a locally advanced stage, and the use of these inhibitors may be necessary to obtain tumour downsizing before surgery [7]. Neoadjuvant treatment in GISTs has been shown to be effective in several studies, but the duration of this treatment has been the subject of debate. We report a good response after 16 months of neoadjuvant therapy with

imatinib in a large atypical stomach GIST, allowing secondary surgical excision

CASE REPORT

A 51-year-old female patient had upper gastrointestinal bleeding with haematemesis and melena in the context of an altered general condition. The physical examination revealed weight loss (15 kg) and an abdominal mass of approximately 20 cm in size on the major axis, located in the epigastrium and left hypochondrium. The mass was not very mobile and was poorly limited. A blood test showed anaemia (8 g/dl). A computed tomography (CT) scan revealed a voluminous mass of approximately 22 cm in size from the rear cavity of the epiploon with a predominant mix of aerobic and fluid components. The mass had a thickened and irregular wall and pushed back the stomach (Fig. 1). This observation was suggestive of a gastric duplication with blocked communication. An oesophagogastroduodenoscopy did not reveal any lesion up to the 3rd duodenum apart from an aspect of extrinsic compression of the anterior side of the cardio-tuberosity junction. An exploratory laparotomy was decided upon, as the ultrasound endoscopy was not available. During this exploration, a large tumour of a suspicious nature was found at the expense of the posterior gastric wall extending from the spleen to the left hepatic lobe and left diaphragmatic cupola. There was no hepatic metastasis, suspicious adenopathy or peritoneal carcinosis. Nevertheless, the lesion seemed to be inextirpable. We therefore ended the procedure by performing, via a short gastrotomy, four biopsies of the lesion that communicated with the gastric lumen through an orifice admitting a finger. The postoperative outcomes were simple. The biopsy results were in favour of a stromal tumour, with positive CD117, CD34 and Dog1 antibodies (Figs. 2, S1, S2 and S3). The Ki-67 index was positive at 4%.

A treatment with imatinib at the initial dosage of 800 mg twice daily was initiated. Poor tolerance to treatment (i.e., severe asthenia and aggravation of anaemia following repeated digestive bleeding) required a reduction in the

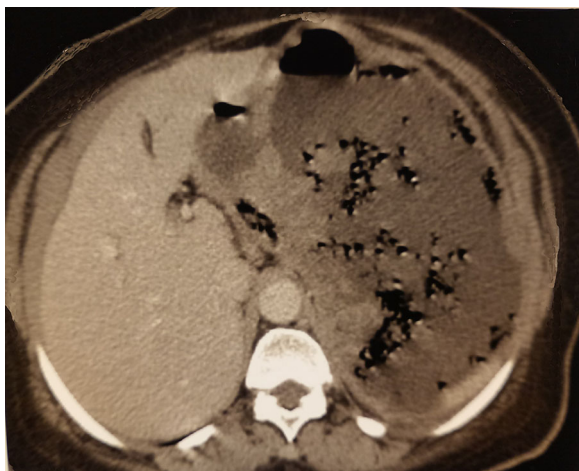


Fig. 1 First CT scan showing the tumour

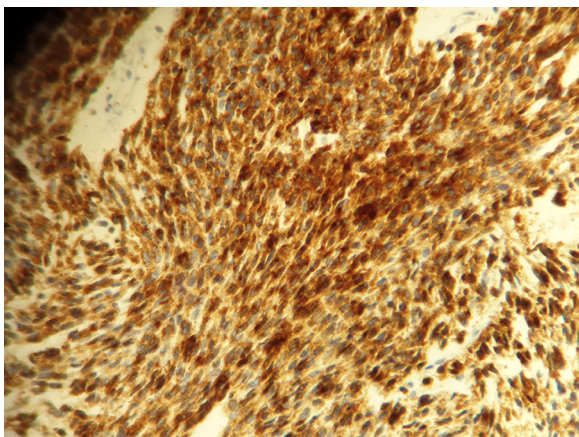


Fig. 2 CD117 positivity on immunohistochemistry

dosage to 400 mg/day and transfusion. Under this treatment, the patient's condition constantly improved, with a regular regression of the mass that was no longer palpable after 16 months of treatment. The total weight gain was then 8 kg. The CT scan showed a partial response with an estimated residual mass of 8 cm on its largest axis (Fig. 3). A second laparotomy was performed after 16 months of imatinib treatment. An en bloc resection made of an upper polar gastrectomy with part of hepatic segment 3 and splenectomy was performed because of residual invasion of the

spleen hilum and left hepatic lobe. Immediate oeso-antral anastomosis was performed at the same time. The outcomes of this operation were simple. The resection was histologically R0. Imatinib treatment was continued at a daily dose of 400 mg. After a 12-month follow-up, no recurrence was noted.

The authors received consent to both publish and participate from the patient. This case also received approval from the head of the Surgery Department of the Sylvanus Olympio University Hospital (Ref. N06/2019/DCS/CHUSO) to be reported and published.

DISCUSSION

Surgery remains the curative treatment of GISTs to this day [3]. However, the surgical option may be reconsidered in the case of a large tumour, which, via its extension to neighbouring organs, may potentially impose organ sacrifice with the risk of not obtaining a negative margin [8], thus posing the problem of resectability. The case we reported fits into this situation, with an unusual predominant mix of aerobic and cystic components, creating additional diagnostic difficulties related to its confusion with gastric duplication. Indeed, the exploration tools at our disposal did not allow us to make a diagnosis, and the predominant cystic component of the tumour increased the risk of tumour rupture in the event of a percutaneous biopsy. Hence, our first laparotomy, the main goal of which was clearly surgical excision for a histological diagnosis on the surgical specimen. The limitation of our objective to perform an exclusively diagnostic procedure in view of the operative findings during this first operation supports the need for a histological diagnosis to plan the management of our patient as well as the need for neoadjuvant therapy for large tumours to obtain downstaging for a better carcinologic result.

The introduction of targeted therapy, including imatinib, whose administration is well codified in adjuvant therapy, has improved patient prognosis [3]. Targeted therapy has provided neoadjuvant perspectives for large tumours with a high risk of malignancy. The

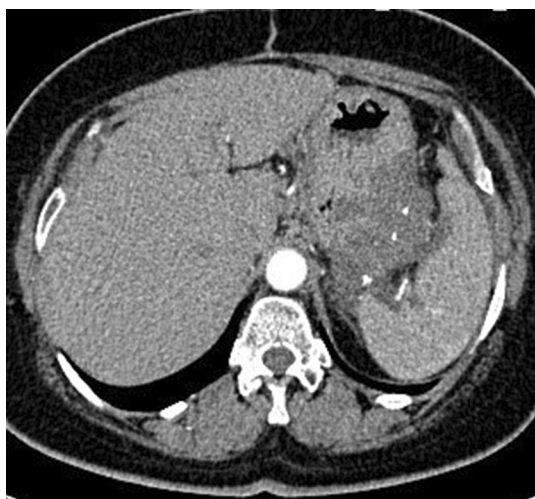


Fig. 3 Tumour aspect on CT scan after neoadjuvant therapy

preoperative use of imatinib in locally advanced GISTs is based on the assumption that in neoadjuvant therapy, imatinib could reduce the risk of tumour rupture and incomplete resections as well as minimise the intraperitoneal dissemination of tumour cells and thus the recurrence rate [8]. In fact, the preoperative use of imatinib is becoming more common, but the duration of this neoadjuvant treatment, which varies from one study to another, remains a point of controversy. Blanke [9] proposed a duration of 3–6 months in a randomized trial. In 2009, the ESMO recommended a duration of 3–12 months until a maximum response was obtained [10]. However, for most studies, the median duration of neoadjuvant treatment is between 6 and 8 weeks and generally does not exceed 1 year [11–17]. These studies remained within these limits based on the idea that the optimal response would be achieved between 4 and 12 months, with a low risk of developing secondary resistance and a better surgical outcome [17].

The extension of this duration to 16 months in our patient was justified by the good clinical response illustrated by the progressive and regular disappearance of the mass on palpation and by an objective response to the control on the CT scan. According to a study by Chaoyong Shen [16], one patient remained sensitive to imatinib after 57 months of treatment,

suggesting that the optimal duration of preoperative treatment may vary from one individual to another. Recent data on the tumour response to imatinib based on the molecular profile of GISTs seem to confirm this interindividual difference in the treatment response by showing a better response of KIT exon 11 and 13 mutations, while KIT exon 9 mutations and PDGFRA gene mutations are associated with a poor response [6]. Furthermore, by comparing the median duration of the neoadjuvant treatments of several series, it appears that a longer duration is associated with a higher resectability rate and, consequently, a better tumour response [11–15, 17].

It can be concluded from the above results that the response to treatment varies from one individual to another and that the longer the duration of neoadjuvant treatment is, the better the tumour response. Regarding the expectation of surgical excision, we believe that the duration of optimal treatment should depend on the tumour response to treatment and be the option that provides better tumour reduction for carcinologic excision.

For very large tumours, the duration of treatment must therefore be extended as long as the tumour responds to treatment, as in our patient, for whom 16 months were necessary. In our opinion, the regular monitoring and, if possible, molecular typing of GISTs are decisive criteria that should be considered in the neoadjuvant treatment of GISTs. Indeed, one of the objectives of follow-up is to identify adverse side effects that may lead to a reconsideration of imatinib dosage, as was the case in our patient. In the context of neoadjuvant therapy, the main objective of follow-up is to assess the response to imatinib therapy, which should be key in decision making to continue or not continue treatment, especially in the absence of molecular typing to predict a tumour response. This response can be evaluated with a CT or PET scan [18]. However, according to the ESMO's recommendations in 2014 [3], PET scans show high sensitivity in the early assessment of the tumour response and could therefore be very useful in neoadjuvant treatment where response prediction is particularly important. However, for regular monitoring, CT is most

commonly used because it provides more anatomical information [19]. We based our follow-up essentially on the clinic because of the difficult accessibility of the CT scan under our working conditions and performed a CT scan only when the mass disappeared after abdominal palpation.

The 16-month neoadjuvant treatment thus allowed tumour removal in two stages. Despite tumour reduction, the persistence of infiltration in the splenic hilum and inferior side of the left lobe indicated splenectomy, and a notch in the left lobe suggested a potential gain in organ preservation if treatment had continued.

LIMITATIONS

For technical reasons, the molecular profile used to determine the type of mutation involved was not performed, although this had little impact on the management of our patient.

CONCLUSION

Neoadjuvant treatment is necessary in patients with large GISTs to achieve tumour downsizing before surgery. The treatment should be continued as long as there is a good tumour response and tolerance to the medication to obtain tumour downsizing compatible with carcinologic excision.

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Disclosures. Fousséni Alasani, Boyodi Tchangai, Aklesso Bagny, Ablavi A Adani-Ife, Kossigan A Amavi, Tchou Darre and Komla Attipou declare that they have no competing interest.

Compliance with Ethical Guidelines. We received consent to both publish and participate from the patient. This case also received approval from the head of the Surgery Department of the Sylvanus Olympio University Hospital (Ref. N°06/2019/DCS/CHUSO) to be reported and published.

Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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REFERENCES

1. Wang L, Liu L, Liu Z, Tian Y, Lin Z. Giant gastrointestinal stromal tumor with predominantly cystic changes: a case report and literature review. *World J Surg Oncol.* 2017;15:220.

2. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med*. 2006;130:1466–78.
3. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014;25(Suppl Suppl 3):21–6. <https://doi.org/10.1093/annonc/mdu255> (Erratum in: *Ann Oncol*. 2015 Sep;26 Suppl 5:v174-7).
4. Joensuu H, Martin-Broto J, Nishida T, Reichardt P, Schöffski P, Maki RG. Follow-up strategies for patients with gastrointestinal stromal tumour treated with or without adjuvant imatinib after surgery. *Eur J Cancer*. 2015;51(12):1611–7.
5. Koo D-H, Ryu M-H, Kim K-M, et al. Asian consensus guidelines for the diagnosis and management of gastrointestinal stromal tumor. *Cancer Res Treat Off J Korean Cancer*. 2016;48(4):1155–66.
6. Nishida T, Blay J-Y, Hirota S, Kitagawa Y, Kang Y-K. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. *Gastric Cancer*. 2016;19(1):3–14.
7. Asif S, Gupta N, Gupta G, Mehta A, Singh S. Effective downsizing of a gastroesophageal GIST using neoadjuvant imatinib mesylate: a case report. *J Gastrointest Cancer*. 2017;48(2):198–200.
8. Wang CY, Ser KH, Kuan WS, Lee WJ. Surgical intervention of a giant gastric gastrointestinal stromal tumor following neoadjuvant therapy with imatinib. *Formos J Surg*. 2018;51:162–6.
9. Blanke CD, Joensuu H, Demetri GD, Heinrich MC, Eisenberg B, Fletcher J, et al. Outcome of advanced gastrointestinal stromal tumor (GIST) patients treated with imatinib mesylate: four-year follow-up of a phase II randomized trial. *AIIn: SCO Gastrointestinal Cancers Symposium Proceeding 2006*; p. abstr 7.
10. Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY, ESMO Guidelines Working Group. Gastrointestinal stromal tumors: ESMO clinical recommendations for diagnosis treatment and follow up. *Ann Oncol*. 2009;20(Suppl 4):64–7.
11. Andtbacka RH, Ng CS, Scaife CL, Cormier JN, Hunt KK, Pisters PW, et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. *Ann Surg Oncol*. 2007;14(1):14–24.
12. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. *J Surg Oncol*. 2009;99:42–7.
13. Hohenberger P, Langer C, Wendtner CM, et al. Neoadjuvant treatment of locally advanced GIST: results of APOLLON, a prospective, open label phase II study in KIT- or PDGFRA-positive tumors. *J Clin Oncol*. 2012;30:abstr 10031.
14. Tielen R, Verhoef C, van Coevorden F, et al. Surgical treatment of locally advanced, non-metastatic, gastrointestinal stromal tumours after treatment with imatinib. *Eur J Surg Oncol*. 2013;39:150–5.
15. Rutkowski P, Gronchi A, Hohenberger P, Bonvalot S, Schöffski P, Bauer S, et al. Neoadjuvant Imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG Experience. *Ann Surg Oncol*. 2013;20(9):2937–43. <https://doi.org/10.1245/s10434-013-3013-7>.
16. Shen C, Chen H, Yin Y, Chen J, Zhang B, Chen Z, et al. Preoperative imatinib for patients with primary unresectable or metastatic/recurrent gastrointestinal stromal tumor. *Clinics*. 2014;69(11):758–62.
17. Ramaswamy Anant, Jain Deepak, Sahu Arvind, Ghosh Joydeep, Prasad P, Deodhar K, et al. Neoadjuvant imatinib: longer the better, need to modify risk stratification for adjuvant imatinib. *J Gastrointest Oncol*. 2016;7(4):624–31.
18. Crosby JA, Catton CN, Davis A, et al. Malignant gastrointestinal stromal tumors of the small intestine: a review of 50 cases from a prospective database. *Ann Surg Oncol*. 2001;8:50–9.
19. Gold Jason S, De Matteo Ronald P. Combined surgical and molecular therapy: the gastrointestinal stromal tumor model. *Ann Surg*. 2006;244:176–84.