Case Report

Strong Long-Term Survival with Targeted Therapy in Inoperable/Metastatic Gastrointestinal Stromal Tumors

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ABSTRACT: Gastrointestinal stromal tumors (GISTs) belong to a group of cancers called soft-tissue sarcomas. Soft-tissue sarcomas develop in the tissues that support and connect the body, including muscles, nerves, tendons and joints. In this paper we report a case of 67-years old man with unresectable GIST and associated liver metastasis who experienced a very good response to Imatinib mesylate (Glivec®) therapy in first line for over 10 years. Even after progression and discovery of liver metastasis, increasing the Glivec® dose proved to be an efficient strategy with no added toxicity and an overall satisfactory quality of life.

KEYWORDS: *GIST, Imatinib, targeted therapy, metastasis.*

Introduction

The origin of GISTs starts in the nerve cells located in the digestive tract. The epidemiology and evolution of GIST is still relatively unknown, with incidence being approximately 11-15 case/mil people/year. They are most common between the ages of 50 and 70, and almost never before the age of 40 [1].

In terms of histology, GISTs are represented by two variants which are often found in mixed forms: the fusiform type which encompasses 70-80% of all tumors and the epithelioid type which encompasses 20-30% [2].

They are frequently very aggressive, with approximately 50% of patients being diagnosed at a metastatic stage of the disease. Regarding the invasion of other organs, the liver is the most affected organ (65% of all cases) and after that the peritoneum (21% of all cases). Additionally, one in three cases of GIST invade adjacent organs. The size of the tumor also correlates with metastatic potential with tumors larger than 10cm having a 86%risk of metastasis [2].

From a biomolecular point of view, GISTs are a distinctive gastrointestinal tumor group with origins in the Cajal interstitial cells (CIC) which play a major role in the control of the intestinal peristaltic movement. CIC abundantly express the c-Kit (CD117)-a tyrosine kinase receptor (RTK) which binds the stem cell factor (SCF) [3,4].

From a clinical point of view, GISTs have a relatively modest proliferation potential and present no specific symptoms if they don't exceed 2cm in size. In the case of larger GISTs (2-30 cm) the most frequent clinical symptom is gastric bleeding. Optimal treatment for resectable GISTs is based on surgery. For unresectable and metastatic stages standard treatment European Society of Medical Oncology (ESMO)/National Comprehensive Cancer Network (NCCN) recommendations standard treatment is based on tyrosine kinase inhibitor (TKIs) such as Imatinib, Sunitinib or Regorafenib [5,6].

Chemotherapy has not proven any notable effect in the treatment of GISTs [7].

Case Study

In this study, we present the case of a 67 years old man (S.T.), diagnosed 10 years ago (26.10.2010) with GIST undergoing treatment with Imatinib mesylate (Glivec®). The patient has signed an informed consent which permits the usage of the information presented in this article for scientific purposes.

The patient was admitted in January of 2010 at the Bucharest Oncology Institute. After the initial diagnosis the patient was monitored at the Alexandria Emergency County Hospital in Alexandria, Romania. At admittance, the patient presented with diffuse abdominal pain, nausea, anorexia, hematemesis, melaena. After the clinical examination an abnormal abdominal mass of approximately 20cm was found in the left hypochondrium.

An exploratory laparotomy was performed with tissue sampling for histopathological and immunohistochemical examination. The histopathological result were: gastric wall section with free glandular mucosa, a proliferation of cells with epithelioid and fusiform appearance, with moderate cell density,

arranged in a loose, edematous vascular stroma is present at the level of the muscularis propria. Tumor cells show reduced atypia, perinuclear vacuolization, no obvious mitotic figures on the examined sections.

The immunohistochemical staining revealed the following: CD 117(+), PDGFR (+), CD34(+), S100(+), EMA (-), KI 67 20-25%.

The corroborated conclusion from the two results were equivocal for a gastrointestinal stromal tumor.

A multidisciplinary team (MDT) was organized and after careful evaluation the diagnosis was established: unresectable stage IIIB(T4N0M0). In accordance with the NCCN and ESMO guidelines, which clearly state that the main treatment option for unretractable GISTs is Glivec®, the patient began therapy with the TKI on 03.06.2011 with a dose of 400mg/day. No noteworthy side effects were observed.

The Computer Tomography (CT) scan described a tumoral mass located in left abdomen with an approximate size of 170/90mm which included small intestines and the pancreas. The tumoral mass was also in contact with the left kidney and anterior abdominal wall, with no secondary lesions (hepatic, bone or pulmonary) (Figure 1).

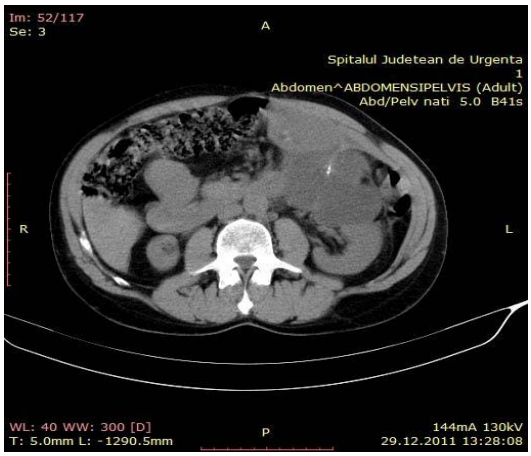

Figure 1. CT Scan of the abdomen-2011; A sizeable tumor is visible in the left abdomen in direct contact with adjacent organs.

After one year of treatment, on 29.12.2012, the periodic evaluation based on a contrast-enhanced CT scan described a mass of 80/30mm, clearly indicating a major regression of the tumor in accordance with RECIST criteria [8], with no signs of pulmonary/ bones/liver metastasis.

After 4 years of treatment, on 15.09.2015 the patient was again evaluated using a contrast-enhanced CT scan. The results indicated a solid tumor mass of 92/40.5mm in comparison with last evaluations and presence of two new hypodense lesions in the liver measuring 11/11mm and 9/9mm, respectively. The conclusions drawn were: progressive disease with secondary liver invasion and no sign of pulmonary/bones secondary lesions.

The MDT took notice of the progressive nature of the tumor and, in accordance with the guidelines published at the time (NCCN and ESMO), decided to increase the daily dose of Glivec® to 600mg/day.

One year after the MDT it was decided to change the therapeutic approach, on 05.10.2017, at the subsequent examination, the contrast-enhanced CT scan presented a tumoral mass of 70/60mm with several internal calcified areas.

The two hepatic micronodules were of the same size when compared with the previous examination. No sign of pulmonary/bones secondary lesions were present at the examination.

Given the results, the MDT team decided that the best course of action is to maintain therapy with Glivec® (Figure 2).

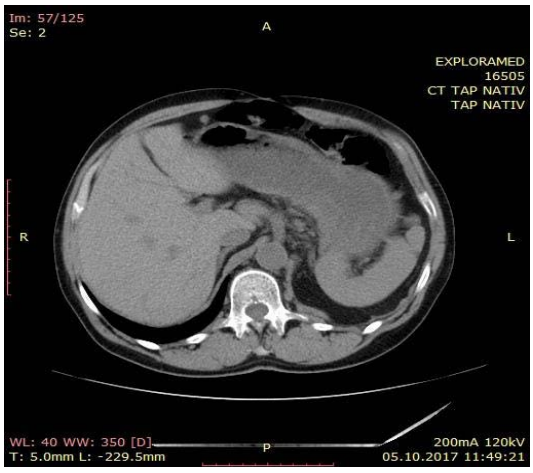

Figure 2. CT Scan of the abdomen-2017; Two secondary lesions are visible in the liver.

Two years after the MDT it was decided to increase the dose of Glivec®, on 13.09.2018, the periodic CT scan evaluation recorded the presence of a solid mass in the left abdominal cavity with approximately the same size (71/40mm), no changes in the proximity with other organs but more importantly with clear areas of calcification in the tumor.

The two liver micronodules are described as haven reduced sizes in contrast with last evaluation. No sign of pulmonary/bone secondary lesions have been recorded (Figure 3).

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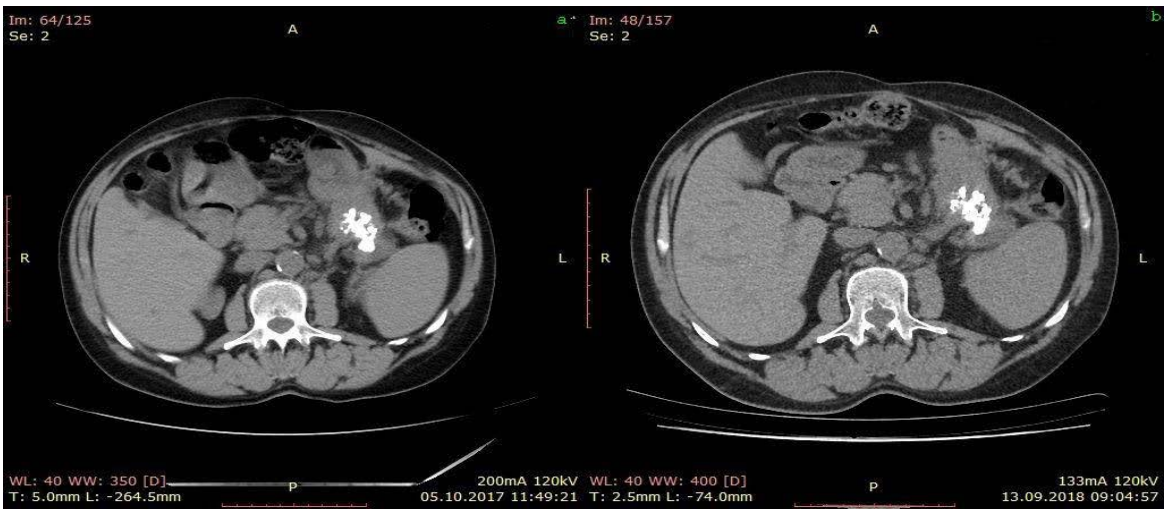

Figure 3. CT Scan of the abdomen-2018; Calcifications are visible inside the tumoral mass. The two secondary localizations are not visible in the liver.

Discussion

GISTs are the most diagnosed neoplasms of the gastrointestinal system [9].

Not long ago, GISTs were considered one of the hardest to treat tumors, given their almost complete innate resistance towards more conventional treatments such as chemotherapy or radiotherapy. More so, GISTs were also poorly defined as distinct entities before the emergence of immunohistochemistry which helped properly distinguish this type of tumor from others. The major breakthrough was identifying the CIC as the precursors of this tumor and also discovering the important roles played by the c-KIT and platelet-derived growth factor receptor a (PDGRF-a) as major drivers of tumoral evolution [10,11].

This discovery helped fuel the first and biggest breakthrough in the fight against GISTs: the addition of Imatinib mesylate. Initially used for stage IV patients, the drug was gradually become standard of care for unresectable non-metastatic, recurrent tumors and also adjuvant and neoadjuvant therapeutic regimens [12-16] and also alongside more novel targeted therapies [12].

This evolution strongly highlights how, within the span of a decade, the introduction of personalized medicine has completely reshaped the therapeutic landscape of a tumor initially considered untreatable [17-19].

In our case report, we aimed to highlight just how much the addition of Glivec® has impacted the therapeutic scope of patients suffering from GISTs. A67 year old patient diagnosed with unresectable GIST presented a grim prospect at the moment of diagnosis. Fortunately, due to the strong potential of Imatinib mesylate (Glivec®) the MDT managed to control the disease for 10 years. Even when facing a potential disease progression and the appearance of liver metastasis, just by increasing the dose of the TKI the MDT managed to halt the tumor's evolution and maintain a satisfactory quality of life for a patient who would previously receive a 6 months survival prognosis before the introduction of Imatinib mesylate.

Conclusion

This 10 year survival is an outstanding achievement in terms of survival, disease control and quality of life for patients with GIST. Glivec® has proven highly effective in the treatment of GISTs showing strong potential for disease control while maintaining an acceptable level of toxicity and an overall good quality of life. This underscores just how much targeted therapy has impacted the clinical management of cancers which were previously considered untreatable.

Abbreviations

Gastrointestinal stromal tumors (GISTs); Cajal interstitial cells-CIC; tyrosine kinase receptor-RTK; European Society of Medical Oncology-ESMO; National Comprehensive Cancer Network-NCCN; Tyrosine Kinase Inhibitor-TKI; platelet-derived growth factor receptor-PDGFR; Multidisciplinary Team-MDT

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Cristian Tuta and Bogdan-Ionel Vatu share equal contributions to this work.

Conflict of interests

None to declare.

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