Complete Pathological Response in Advanced Extra-gastrointestinal Stromal Tumor After Imatinib Mesylate Therapy: A Case Report

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Abstract. Background: Gastrointestinal stromal tumors are uncommon intra-abdominal tumors. In fewer than 5% of cases, they originate primarily from the mesentery, omentum or peritoneum and these extra-gastrointestinal stromal tumors tend to have characteristics similar to gastrointestinal stromal. Case Report: We report a case of extra-gastrointestinal stromal tumor in a 76-year-old male, Eastern Cooperative Oncology Group (ECOG) performance status of 2. Abdominal Computed Tomography (CT) showed multiple non-homogeneous confluent nodules at the level of the greater omentum and mesentery, involving the bladder and rectum, with additional peritoneal nodules in the upper abdomen. In March 2008, the patient started imatinib mesylate at 400 mg/day. Instrumental examinations showed progressive response until thoracic-abdominal CT in February 2012 which documented a complete response. Follow-up ended in October 2013. Treatment with imatinib, in addition to pathological response, provided clinical benefit, a progressive regression of symptoms and improved the patient’s ECOG performance status from 2 to 0.

Gastrointestinal stromal tumors are uncommon mesenchymal spindle-cell or epithelioid neoplasms that arise mainly in the stomach (60-70%) and the small intestine (20-30%) (1); they are rarely located in the colon (1-2%), rectum (3-5%) and esophagus (<2%). Gastrointestinal stromal tumors represent the majority of primary non-epithelial neoplasms of the digestive tract. In <5% of cases they originate from other intra-abdominal tissues and are called extra-gastrointestinal stromal tumors (EGISTs) (2, 3). These extra-gastrointestinal stromal tumors tend to be more common in patients over the age of 50 years, with median age at diagnosis being approximately 60 years, and they are slightly more prevalent in males than in females. Extra-gastrointestinal stromal tumors are tumors with overlapping immunohistological features, occurring in the abdomen but outside the gastrointestinal tract, such as the omentum (80%), mesentery and retroperitoneum, with no connection to the gastric or intestinal wall.

The molecular pathogenesis of gastrointestinal stromal tumor is usually driven by activating mutations of the V-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog (KIT) gene that encodes the cluster of differentiation-117 (CD117) oncoprotein, a transmembrane tyrosine kinase receptor for stem cell factor (4). Although their histological appearance and immunophenotype are as a rule identical to those of classical gastrointestinal stromal tumors, the origin of extra-gastrointestinal stromal tumor is uncertain. They are thought to arise from a common precursor of the Cajal interstitial cells because they both express CD117, a protein transcribed from the c-KIT gene (2, 5). Extra-gastrointestinal stromal tumors tend to have similar characteristics to gastrointestinal stromal tumors (6). Our knowledge on extra-gastrointestinal stromal tumors is based on accumulated data from individual case reports.

In this article, we describe a long-term complete pathological response of an extra-gastrointestinal stromal tumor to imatinib.

Case Report

In February 2008, a 76-year-old man presented with lower abdominal pain, postprandial bloat and constipation. Abdominal Computed Tomography (CT) scan revealed multiple non-homogeneous confluent nodules at the level of the greater omentum and the mesentery, determining the
appearance of an extensive abdominal and pelvic mass, with heterogeneous contrast enhancement involving the dome of the bladder and the anterior wall of the rectum. Additional peritoneal nodules in the upper abdomen and one non-homogeneous nodule of 2.5 cm at the level of the posterior-lateral wall of the rectum were also revealed (Figure 1). Histology of the needle biopsy of a peritoneal nodule indicated a mesenchymal tumor with mixoid stroma (extra-gastrointestinal stromal tumor), which was CD117⁺, anti-cytokeratin AE1/AE3 antibody⁻, calretinin⁻, muscle-actin-specific monoclonal antibody HHF35⁻, α-actin antibody (1A4)⁻, carcinoembryonic antigen (CEA)⁻, protein S100⁻ and mindbomb E3 ubiquitin protein ligase 1 (MIB1)⁺ in 20% of cancer cells. The patient had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2. In March 2008, the patient started imatinib mesylate at 400 mg/day. The thoracic-abdominal CT of May 2008 documented a reduction in size of the non-homogeneous solid mass (10×6.5 cm), reduced size and number of the multiple omental, mesenteric and peritoneal nodules, the largest with a dimension of 4×2.5 cm (Figure 2). The fluorodeoxyglucose positron-emission tomographies (FDG-PET) performed in September 2008, November 2009 and November 2011 showed the absence of disease sites with high glucose metabolism. The patient continued imatinib therapy and subsequent CT scans showed the disease responding with a progressive reduction in lesion size until the thoracic-abdominal CT of February 2012 (Figure 3) documented a complete response with the absence of any disease sites, confirmed by subsequent instrumental examinations. Follow-up of the patient ended in October 2013.

**Discussion**

Extra-gastrointestinal stromal tumors are managed using a multidisciplinary approach. Mutational analysis (KIT/platelet-derived growth factor receptor A (PDGFRA) receptor mutations) has predictive value for sensitivity to targeted molecular therapy, as well as prognostic value, so that its inclusion in the diagnostic work-up of all gastrointestinal stromal tumors is recommended (2). Patients with exon 11 KIT mutations have been found to have the best response to imatinib, better than those of patients with exon 9 KIT mutations (5).
There are few data regarding the clinicopathological factors of extra-gastrointestinal stromal tumors that predict the patient’s prognosis. In a study by Reith et al., 39% of patients with extra-gastrointestinal stromal tumor had an adverse outcome, which suggests that extra-gastrointestinal stromal tumor are aggressive and similar to gastrointestinal stromal tumors located in the distal gastrointestinal tract (3). It was suggested that extra-gastrointestinal stromal tumors that originate from a mesenteric location are more aggressive and similar to small intestinal tumors. Standard treatment of localized (extra-)gastrointestinal stromal tumor is complete surgical excision associated (or not) with adjuvant imatinib therapy.

When primary surgical resection is not possible, targeted therapy with imatinib is indicated. Imatinib is an inhibitor of the tyrosine kinase activity of c-KIT, and has revolutionized the outcome of this disease, raising the median overall survival from 12-24 months to 5 years. The recommended first-line treatment of advanced extra-gastrointestinal stromal tumor is 400 mg/day imatinib (7, 8).

Only 0-4% of patients experience a complete response and most have a partial response, or response without a dimensional component (7). Therapy should be continued indefinitely in the absence of progression or serious side-effects. Suspension leads inevitably to disease progression.

Imatinib is generally well tolerated (7). Toxicity may require dose reduction or temporary suspensions, with a return to the active dose once the side-effects are overcome (9).

Our case illustrates complete remission in a patient who received only imatinib as treatment, so we suppose that our patient has certain mutation conferring a high sensitivity to this therapy. The treatment with imatinib, in addition to producing a pathological response, clinically benefited our patient, with continuing symptom relief and improved ECOG performance status from 2 to 0.

Our study of the literature indicates few published clinical cases of complete pathological response after imatinib therapy for locally advanced or metastatic gastrointestinal stromal tumors (10, 11).

Acknowledgements

We thank the patient and his family. Editorial assistance was provided by Grazia Cini Ph.D. and writing support by Mary Forrest Ph.D. The study was partially funded by Associazione Toscana Ricerche e Cure Oncologiche, Florence, Italy.

References