Two Cases of Complete Response after Imatinib Mesylate Treatment of Advanced GIST

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Abstract. Background: Imatinib mesylate has undoubted efficacy in the treatment of advanced gastrointestinal stromal tumors (GISTs), but complete responses have only been reported rarely. Case report: A 47-year-old man with liver metastasis from GIST achieved a complete response after 7 months of treatment with imatinib and a 47-year old woman with local relapse of GIST on the stomach after gastrectomy, showed complete remission, 9 months after treatment with imatinib. Conclusion: Although the response rate is high in patients with advanced GIST treated with imatinib mesylate, complete responses remain rare. Several issues concerning its optimal administration need to be clarified, in order to improve its efficacy.

One of the most successful therapies that revolutionized modern solid tumor oncology in the treatment of gastrointestinal stromal tumors (GISTs) is imatinib mesylate. When unresectable, GISTs were, until five years ago, resistant to any type of treatment. Imatinib mesylate is the only drug, which prolongs survival in advanced GISTs, but complete responses to this drug are rare. Two cases of complete response to imatinib mesylate are reported here.

Case 1

A 47-year old man, with a history of H. pylori gastritis, presented with epigastric pain. In April 2003, a computed tomography (CT) of the abdomen showed a 5cmx5.5cm area arising from the anterior wall of the stomach. He underwent a partial gastrectomy and the pathology showed a GIST positive for CD117, focally positive for actin and very sparsely positive for S-100. In addition, in surgery, small nodular lesions were found on both lobes of the liver. Biopsy taken from one of them was positive and consistent with GIST. Following the operation, MRI of the abdomen revealed some simple cysts and metastatic lesions found during the operation on the liver. The patient was then administered imatinib mesylate (400 mg per day). In August 2003, an MRI of the abdomen showed partial response of the hepatic metastatic lesions, while in December 2003 the MRI was negative for metastatic lesions. The treatment continued for 18 months in total and the patient was then put on follow-up every 3 to 4 months. The patient remains in complete response and the liver ultrasound in April 2005 and the MRI in June 2005 showed no metastatic lesions (Figure 1).

Case 2

A 47-year-old woman, with a history of heterozygous beta-thalassemia, palpated an epigastric mass, in December 2002, which, on abdominal CT scan, seemed to arise from the stomach. The patient underwent a partial gastrectomy for a huge mass, measuring 18cmx11cmx4cm, found on the great curvature of the stomach. Pathology revealed a GIST positive for CD117, CD34 and vimentin and negative for actin, desmin and S-100 protein, with necrosis, high mitotic rate and a high percentage of Ki-67 positivity. Two months later, the abdominal CT scan revealed an abnormal finding, arising from the stomach and extending to the abdominal wall, which was consistent with local relapse. She was then treated with 400 mg per day imatinib mesylate. In August 2003, the disease remained unchanged on CT scan and the dose of imatinib was increased to 600 mg per day. Three months later, this abnormal finding disappeared on CT scan and since then, she has remained disease-free, while the patient has been on treatment with imatinib (Figure 2).
Discussion

GISTs are a subgroup of soft-tissue sarcomas that arise in the gastrointestinal tract, usually the stomach and small intestine. These tumors are thought to be derived from the cells of Cajal, which have an important role in the regulation of gastrointestinal tract motility and are usually called "pacemaker" cells. The prevalence of GISTs is 15-20 per 1,000,000. Due to their unresponsiveness to chemotherapy or radiotherapy, advanced GISTs had very poor prognosis until recently, when they were found to express the mutated KIT receptor or the mutated platelet-derived growth factor receptor α (PDGFR-α). These receptors are the targets of the very effective drug, imatinib mesylate. Various mutations of the KIT receptor have been described in GISTs, especially the mutation in exon 11, which seems to be prognostic (1, 2), although these mutations have also been found in other neoplasms with unknown clinical significance (3).

In February 2002, imatinib mesylate was approved by Food and Drug Administration (FDA) for the treatment of advanced GISTs (4), as a result of its high efficacy shown in a phase II trial (5). The recommended dose was 400 or 600 mg per day. Since then, several trials were published with response rates ranging between 44 and 71% (5-13), but complete responses were rare, ranging between 3...
and 10% (6-9). In addition, it is only recently that complete responses tend to occur. In a recent large trial (6), the median time to complete response was 7 months (210 days), approximately twice as that of the median time to the best response (91-113 days) (5, 6, 8). In a randomized trial conducted by Verweij et al. (6), although most responses occurred within 9 months from the onset of treatment, the best responses were observed even 2 years after the beginning of the treatment. Therefore, the time of follow-up should be high enough to demonstrate complete responses. In accordance with these findings, complete responses were reported in trials with prolonged follow-up time (median 760 to 768 days) (6, 8). In contrast, Demetri and colleagues did not report any complete response after a median follow-up time of only 288 days (5). In our cases, the time to complete response was 7 months for the first patient and 9 months for the second.

Doses of imatinib ranging between 400 to 1000 mg daily were used in various clinical trials and 800 mg were defined as the maximum tolerated dose. In two recently published large randomised phase III trials (6, 8), the complete response rate was the same in the group of patients taking 400 mg of imatinib daily and those taking 800 mg of imatinib (3-6%). In the former trial (6), a slightly better time-to-progression was reported in the group taking 800 mg of imatinib (56% vs. 50% after 760 days of median follow-up), while in the latter trial (8) there was no statistical difference in disease-free survival (50% vs. 53% after 2 years of median follow-up). Although the optimal dose of imatinib is controversial, there is universal agreement that patients who do not respond to 400 mg imatinib daily should be treated with a higher dose, i.e., 800 mg per day maximum, if these are well-tolerated. In approximately one-third of the patients, disease stabilization can be achieved by increasing the dose of imatinib, while partial responses are rare and complete responses have never been noted (5, 8, 10). In our report, the dose of imatinib was increased in the second patient from 400 mg to 600 mg daily, because stability of the disease and complete response were achieved within 3 months. There is no such a case reported in the literature, since in current practice the dose of imatinib is usually increased after disease progression. Therefore, the question arises as to whether patients, who do not respond to or tolerate imatinib well, should try higher doses of the drug or not.

How long should imatinib be given in patients responding to it? Imatinib has dramatically changed the prognosis of these neoplasms, therefore it is difficult to interrupt its administration even in patients achieving complete responses. Recent consensus guidelines support this practice. In a randomized trial, imatinib interruption after one year was associated with a high risk of relapse, even for patients with complete response (9). In conclusion, the drug should not be discontinued, unless progression of the disease or unacceptable toxicity appears. In our study, the first patient discontinued treatment after 18 months and remains in complete response and the second has been under treatment for more than two years with excellent tolerance.

Another interesting observation is that patients who achieved a complete response did not have better disease-free survival than those who obtained a partial response (6, 8). A possible reason could be that GISTs, when responding, often display central necrosis, which could explain the reported pathological complete responses, without concomitant disappearance of radiological findings (13, 14). Responding lesions can also initially remain stable or increase radiologically in size, because of intratumoral hemorrhage, edema or development of myxoid degeneration and decrease in size, after several months of treatment. In this way, new lesions found on follow-up could represent responding metastatic disease, not initially visible with current techniques (15). These observations encouraged many researchers to believe that RECIST criteria are not adequate to describe the whole spectrum of responses to imatinib (13) and other parameters should be considered, such as HU (Hounsfield units) reduction assessment on CT, to avoid unjustified treatment interruption (15). An invaluable tool seems to be FDG-PET scan, because SUV (standardized uptake value) reduction was shown to be able to predict response, even 8 days after the initiation of treatment (12, 16).

Although imatinib has an undoubted efficacy in the treatment of advanced GISTs, many issues must be resolved, such as the optimal dose, the duration of treatment, the methods of the response assessment and the role of adjuvant administration of imatinib, when complete resection of the primary tumor has been carried out. The rarity of these neoplasms intensifies the need to enroll as many patients as possible, in carefully designed multicenter clinical trials.

References


