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Subdural hematoma during therapy of gastro-intestinal stromal tumor (GIST) with Imatinib mesylate

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Abstract

Imatinib mesylate is a widely used tyrosine-kinase inhibitor (TKI) in chronic myeloid leukemia (CML) treatment. Imatinib has contributed to complete and prolong cytogenetic responses so that it is now the standard treatment of CML. Recently, Imatinib mesylate has shown a significantly prolonged progression-free survival and overall survival in metastatic and locally advanced c-Kit positive gastro-intestinal stromal tumors (GISTs) and more recently a prolonged disease-free survival in operated high risk GIST. Imatinib is a well-tolerated treatment with few side effects mainly gastro-intestinal symptoms (nausea, vomiting and diarrhea), headaches, rash and periorbital edema. Hemorrhage incidents are rare in patients treated with Imatinib. They are more frequently seen in CML patients. Hemorrhage incidents in CML include in many cases upper gastro-intestinal (GI) tract bleeding and central nervous system bleeding in rare ones. In GIST patients treated with Imatinib, hemorrhage incidents are exclusively made of upper GI tract bleeding consecutive to tumor perforation or necrosis. In our observation, we present the case of a subdural hematoma occurring in a patient treated with adjuvant Imatinib for a high risk localized gastric GIST. No other case of subdural hematoma in GIST treated with Imatinib has been reported in literature.

Keywords:
Subdural hematoma, Imatinib mesylate, side effects, GIST.

Background

Imatinib mesylate is a tyrosine kinase inhibitor (TKI) drug initially used in chronic myeloid leukemia (CML) through selective tyrosine kinase suppressive activity of the BCR-ABL. GISTs are the most common malignant mesenchymal tumor of the gastro-intestinal tract. The c-kit (CD117), a tyrosine kinase receptor, is present in about 95% of GIST. Through the TKI activity of the c-kit receptor and also the PDGFRA (platelet derivate growth factor receptor A), Imatinib is now the leading drug in locally advanced or metastatic GIST treatment and have recently shown a significantly longer progression-free survival in the adjuvant treatment of high risk operated GIST.

Imatinib therapy is usually well tolerated; side effects are mainly exhibited through gastro-intestinal toxicities. Central nervous system (CNS) hemorrhage incidents are very rare during treatment with Imatinib, especially in GISTS. In this article, we present the case of subdural hematoma occurring during Imatinib adjuvant therapy of gastric stromal tumor.

Observation

A 44-year-old male with history of hypertension under treatment, consulted in April 2009 for an abdominal pain with melena. Gastroscopy showed a fundic sub mucosal tumor process. Biopsy with histopathological study of the tumor revealed c-kit positive gastric stromal tumor. Chest x-ray and abdominal ultrasound showed no metastasis. Patient underwent a total gastrectomy. Definitive pathological study of tumor resection found a c-kit positive stromal...
tumor, measuring 10 cm with high mitotic count (15 mitoses/50 CFG). According to Miettinen classification, tumor was considered a high risk of relapse (10 cm size and high mitotic count) and an Imatinib adjuvant therapy at the dose of 400 mg/day was indicated for the patient.

Imatinib therapy started in May 2010. Six months later, a first control did not find any side effects with a controlled disease (no loco regional or metastatic relapse). Ten months after treatment began, the patient presented an unbearable headache quickly followed by loss of consciousness. Cerebral CT scan revealed a subdural hematoma. He had no history of prior traumatic events or of anti-coagulation medication. He was subsequently transferred to neurosurgical unit for hematoma evacuation. Patient died one day after subdural hematoma evacuation.

Discussion

Imatinib mesylate is one of the leading drugs in the targeted therapies era. Its TKI activity yielded to complete and durable cytogenetic complete remission through suppression of BCR-ABL in leukemic cells (1). Locally advanced and metastatic GISTs, known to be chemo resistant tumors, had been successfully treated with Imatinib (3) with a significantly prolonged overall survival and progression-free survival. This is due to a selective inhibitory action on the c-kit tyrosine kinase receptors (CD117) found in about 95% of GISTs and also due to its inhibitory action on PDGFRA (platelet derivate growth factor receptors) (3). Recent studies showed that high risk operated GIST (according to the AFIP classification based on tumor site, mitotic count and tumor size) benefit from Imatinib adjuvant therapy resulting in a significantly reduced relapse rate (2).

Imatinib therapy is generally well tolerated. Most common side effects include intestinal toxicities (vomiting, nausea and gastric pain), periorbital edema, headache and sometimes liver enzymes disturbances (1). These effects rarely induce a treatment arrest and do not need any symptomatic therapies. Imatinib mesylate have also hematological toxicity which occurs much more during CML treatment than during GIST (1). Imatinib hematological toxicity is of two types: bone marrow toxicity (anemia, leucopenia and/or thrombocytopenia) and hemorrhage incidents. During CML therapy with Imatinib, hemorrhage incidents include CNS hemorrhages and gastrointestinal bleedings generally consecutive to thrombocytopenia; while during GIST treatment, hemorrhagic incidents are almost represented by upper GI tract bleedings consequently to Imatinib induced tumor necrosis or perforation (5, 6). Imatinib can induce minor hemorrhagic incidents such as ocular conjunctive hemorrhage(6).

Anticoagulation medication, previous thrombocytopenia and impaired platelet aggregation or coagulation system dysfunction are admitted risk factors of Imatinib hemorrhagic toxicity (5, 6). Our observation is about a young adult taking 400 mg/day of Imatinib mesylate as adjuvant treatment for a resected high risk gastric stromal tumor (according to Miettinen classification); this patient developed a subdural hematoma after ten months of Imatinib. Our patient did not take any anticoagulation medication, had no history of cranial trauma and was not known to be carrier of platelet or coagulation dysfunctions.

Subdural hematoma incidence is about 1-15 cases/100,000 population (8). CNS hemorrhagic events consecutive to Imatinib therapy are exclusively reported in CML patients: they occur in 5% of those in blast crisis, 1% of those in the accelerated phase and in 0.6% of those in chronic phases (5).

In a prospective study, M. Usman et al (3) found 5 hemorrhagic events in 232 Imatinib treated patients (219 cases of CML and 13 cases of GIST). These events were as follows: 1 case of epistaxis, 3 cases of conjunctive hemorrhage and 1 case of intra cerebral hemorrhagic accident. All these events were reported in CML patients. The case of intra cerebral hemorrhagic accident occurred during the CML accelerated phase.

Data has shown that from 12500 registered CML patients treated with Imatinib, only 59 patients (0.47%) experienced CNS hemorrhagic events. Fifty-three from these 59 cases had CML
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at an advanced stage and all were receiving more than 400 mg/day of Imatinib mesylate \(^{(5)}\).

M.S. Kim et al reported a case of subdural hematoma occurring in a 33-year-old female treated with Imatinib at 600 mg/day for CML in chronic phase \(^{(8)}\). The patient had headache in the 2 weeks previous to the accident; headache becoming unbearable, a cerebral CT scan has been performed showing a subdural hematoma. This was attributable to Imatinib therapy as there is no prior cranial trauma history, patient did not take any anticoagulation medication, absence of thrombocytopenia or coagulation tests impairments and finally the spontaneous hematoma regression after Imatinib therapy interruption.

In a retrospective series of 121 CML patients treated with Imatinib, K.W. Song et al \(^{(5)}\) described seven cases of subdural hematoma. All seven patients have headaches in the week preceding the hemorrhagic event with loss of consciousness in 5 cases. Imatinib was taken at a dose of 600 mg/day by the seven patients. Three from seven have thrombocytopenia, two patients received antiplatelet medication (aspirin and clopidogrel) and one patient was at blast crisis.

Hemorrhagic events occurring in CML patients treated with Imatinib can be explained in great part by the anti-tumor action of this treatment on leukemic cells, so that Imatinib induces a direct bone marrow toxicity. This hematological toxicity is mainly dangerous when it causes thrombocytopenia and by consequence possibility of hemorrhagic accidents \(^{(5,6)}\).

Thrombocytopenia is not the only offending mechanism of Imatinib hematological toxicity. Imatinib can induce some disturbances in the coagulation system such as low α2 anti plasmine serum level \(^{(8)}\) and also platelet aggregation dysfunction.

A. Quintas Cardama et al \(^{(7)}\) tested platelet aggregation after stimulation test with arachidonic acid and epinephrine in 91 patients with CML in chronic phase either off-therapy or receiving a tyrosine kinase inhibitor including Imatinib. No patient had thrombocytopenia during the test. In this interesting study, ten of the fifteen patients receiving Imatinib have a disturbed stimulation test and this was independent from the treatment dose (400, 600 or 800 mg/day) \(^{(7)}\).

The majority of Imatinib related hemorrhagic events were reported in CML patients. Those occurring in GIST patients are much rare. This can be explained by three facts: first, the little number of GIST patients receiving Imatinib compared to CML patients; second, a much longer period of treatment with Imatinib for CML (lifelong treatment) and finally the completely different anti-neoplastic mechanisms of Imatinib between CML and GIST.

G. Demetri et al \(^{(4)}\) studied prospectively 147 cases of locally advanced or metastatic GIST treated with two schedules of Imatinib (73 receiving 400 mg/day and 74 receiving 600 mg/day) and focused on hematological and non-hematological toxicities. In this series, 8 hemorrhagic events have been reported: 4 cases of intra tumoral hemorrhage and 4 cases of upper GI tract bleeding. No intra cerebral hemorrhagic event had been reported in this series.

To our knowledge, no other case of CNS hemorrhagic event had been described with Imatinib in GIST treatment.

In our observation, the subdural hematoma was attributed to Imatinib therapy since the patient did not take any anticoagulation medication, had no history of cranial trauma and was not known to be carrier of platelet or coagulation dysfunctions.

Hemorrhagic events occurring in GIST patients treated with Imatinib are exclusively represented by gastro intestinal bleedings and this is due to tumor necrosis or perforation \(^{(4,9)}\). The TK suppressive activity of the PDGFRA, inducing consequently platelet aggregation impairment, may explain some hemorrhages occurring in GIST treated with Imatinib \(^{(6)}\).

**Conclusion**

Hemorrhagic events related to Imatinib are rare (about 2%). In CML treated with Imatinib, gastro intestinal bleedings are the most common followed by CNS hemorrhages. Subdural hematoma is a serious treatment complication
as it can lead to patient death. Usually, subdural hematoma is preceded by headaches which evolve to loss of consciousness. Many factors can explain hemorrhagic accidents in Imatinib therapy; thrombocytopenia is the major factor in addition to alteration of platelet aggregation and coagulation system dysfunction. No other case of subdural hematoma had been described in GISTs treated with Imatinib.

References


