Imatinib mesylate induces responses in patients with liver metastases from gastrointestinal stromal tumor failing intra-arterial hepatic chemotherapy

ABSTRACT

Background: Imatinib mesylate represents a real major paradigm shift in cancer therapy, targeting the specific molecular abnormalities, crucial in the etiology of tumor. Intra-arterial hepatic chemotherapy (IAHC) followed by embolization, has been considered an interesting palliative option for patients with liver metastases from gastrointestinal stromal tumor (GIST), due to the typically hypervascular pattern of the tumor.

Aims: We report our experience with IAHC followed by Imatinib mesylate, in order to show the superiority of the specific molecular approach in liver metastases from GIST.

Materials and Methods: Three patients (pts) with pretreated massive liver metastases from GIST, received IAHC with Epirubicin 50 mg/mq, every 3 weeks for 6 cycles. At the evidence of progression, they received Imatinib mesylate.

Results: We observed progressive diseases in all cases. In 1998, one patient underwent Thalidomide at 150 mg orally, every day for 4 months, with evidence of stable disease and clinical improvement. In 2001, two patients received Imatinib mesylate at 400 mg orally, every day, with evidence of partial response lasting 18+ months and 16 months. One of them had grade 3 neutropenia, with suspension of therapy for 3 weeks.

Conclusion: No patient treated with IAHC, reported objective responses, but two of them obtained partial response after the assumption of Imatinib mesylate and one showed temporary stabilization with thalidomide. Imatinib mesylate represents a new opportunity in GIST therapy, targeting the specific molecular alteration. It seems to be superior to conventional intra arterial hepatic chemotherapy.

KEY WORDS: Liver metastases, GIST, imatinib mesylate, intra arterial hepatic chemotherapy.

INTRODUCTION

In the early eighties, Schaldenbrand and Appelman introduced the term “stromal tumor”, to refer collectively to a subset of mesenchymal tumors, referred to by several definitions, with respect to neurogenic or myogenic differentiation.[1] Gradually, the definition, ‘gastrointestinal stromal tumor’ (GIST) came into widespread use and we now know that the cells in GIST have characteristics similar to those of the interstitial cells of Cajal, or pacemaker cells, which have a neuromotor role in normal gut motility. These cells are characterized by expression of KIT. An immunohistochemical marker (CD 117) for KIT, is now being used by pathologists to distinguish GIST from non-GIST spindle tumors, in the gastrointestinal tract. Mutations in the KIT gene lead to overexpression of the tyrosine kinase KIT protein. Heightened tyrosine kinase activity, appears to drive the neoplastic growth of GIST.[2]

Imatinib mesylate inhibits KIT tyrosine kinase activity, enabling an attack on a specific molecular target in GIST. Recent clinical trials resulted in significant remissions of metastatic GIST, a tumor that was resistant to all previous forms of chemotherapy.[3,4] Before the Imatinib mesylate era, surgical resection was the mainstay of therapy for GIST. The primary goal of surgery was complete resection of disease, with avoidance of tumor rupture. After complete resection, the standard of care was observation; neither radiotherapy or chemotherapy had any verified value as adjuvant therapy. In metastatic GIST, the response rate to chemotherapy is extremely low (<10%).[5] Intra-arterial hepatic chemotherapy (IAHC) with embolization, has been judged an
attractive palliative option for patients with liver metastases from GIST, because the tumor is typically hypervascular.\textsuperscript{[6,7]} There is no experience of IAHC based on Epirubicin, a chemotherapeutic agent considered very active in sarcoma.

We present three patients with liver metastases from GIST, failing Epirubicin, given as IAHC. One had stabilization with Thalidomide and two of them obtained a significant evidence of response with Imatinib, showing the superiority of the specific molecular approach than conventional DNA directed chemotherapy.

**CASE REPORTS**

Three patients received surgical therapy for GIST: Radical gastrectomy in case 1, ileal resection in case 2 and left hemicolecotomy in case 3, without evidence of residual disease. Due to tumor size two of them received adjuvant chemotherapy with six cycles of Ifosfamide and Epirubicin.

At liver relapse, they received laparotomy, with debulking of liver metastases and arterial port implant. The tip of the catheter was placed in the gastro-duodenal artery. The functioning of the device and the liver perfusion were checked before every cycle of treatment by angiography.

IAHC consisted of Epirubicin 50 mgr/mq, given as a 30 minutes infusion on outpatient basis every 3 weeks for 6 cycles. Ultrasounds and CT scan have been carried out at the end of treatment.

Our three patients showed evidence of progressive disease, with increase of all lesions and appearance of new deposits in the liver and peritoneal spreading. Performance status was stable in case 1 and worsening in case 2 and 3, moving from 0 to 2 (WHO criteria)

**Case 1**

A 58-year-old woman received thalidomide for 6 months, with clinical improvement and stabilization of disease. This happened in 1998, before the Imatinib era. The patient deceased with large liver and peritoneal nodules, 26 months from primary surgery and 14 months from IAHC.

**Case 2**

A 69-year-old woman underwent ileal resection with omentectomy on December 1999, because of a 25 x 16 cm GIST. She subsequently received adjuvant chemotherapy with Ifosfamide and Epirubicin, until April 2000.

On April 2001, a 12x10 cm solid mass was noted at follow up, in the left iliac region. The following month, she underwent excision of the mass and multiple peritoneal recurrences. Histologic samples were submitted elsewhere for c-Kit determination with negative results and she did not receive any treatment until May 2001, when a 2cm hepatic recurrence and peritoneal multiple implants were evidenced. Second line chemotherapy by Cisplatin and Etoposide was started, but on October 2001 CT scan evidenced that the lesion had increased to 5 cm. In November 2001, the patient was referred for IAHC with Epirubicin, again without benefits, as in January 2002. The lesion was of 9 cm. Histologic samples were submitted for a second opinion and for monoclonal antibody CD117 definition. A clear c-kit positivity was evidenced. Imatinib treatment promptly started at the dose of 400 mg/daily.

After one month of therapy, the lesion was of 7 cm, after five months 5 cm, after eighth months 5 cm. Side effects were: neutropenia grade 4 after 12 weeks of therapy, which disappeared after transient Imatinib withdrawal and cutaneous rash, which resolved with dosage reduction. She is currently well on Imatinib therapy.

**Case 3**

A 63-year-old man underwent left hemicolecotomy in 1999, because of GIST [Figure 1]. One year later, hepatic metastasectomy was performed because of recurrence. On March 2001, he was firstly seen because of further hepatic multiple nodules, up to 2 cm in both lobes and received chemotherapy by Ifosphamide and Epirubicin. Two months later, progression was observed and the patient was shifted to Etoposide and Cisplatin, without any significative improvement. In October, histologic review showed monoclonal antibody CD117 positivity. From January 2002, treatment with Imatinib was started, at 400 mg daily. At this time, CT scan showed multiple hepatic lesions up to 55 mm in diameter. Two months later, echography showed unchanged volume, with cavitation of neoplastic nodules. Recently, CT scan has shown progression, but the patient is still well and asymptomatic. He is now receiving Imatinib.

**Figure 1:** GIST, histologic section showing typical morphology and rare mytosis, 20x
Ng et al, reported only 10% of patients as disease free, after extended follow-up.[10] De Matteo et al, reported that 32 out of 80 patients (40%) presenting primary disease, who underwent complete gross resection, developed recurrent disease at a median follow-up of 24 months. The site of first recurrence in 27 cases, was the liver in nearly two-thirds and peritoneum was involved in about half of the cases.[11]

IAHC has been considered effective in GIST, because the tumours are typically hypervascular. In an initial study, 14 patients with GIST, metastatic to the liver, were treated with hepatic infusion of Cisplatin, mixed with polyvinyl alcohol sponge particles, followed by intra-arterial delivery of Vinblastine. Ten patients (70%), had a partial response lasting from 8 to more than 31 months (median 12 months).Toxicity was significant and included upper right quadrant pain, elevated hepatic enzyme levels, ileus and mild myelosuppression. In a second, recent report of chemoembolization of liver metastases from GIST,[7] 11 patients with metastatic GIST underwent chemoembolization with cisplatin, doxorubicin, mitomycin C, ethiodol and polyvinyl alcohol particles, 1 to 5 times, at approximately monthly intervals. The partial response rate of 16 patients with liver metastases from sarcoma, 11 of whom had GIST, was 13%. Stable disease status was achieved in an additional 69% of patients. The median time to progression was 8 months, postembolization syndrome was common and severe, but no deaths occurred in the first 30 days after embolization. It is not clear whether the results of IAHC combined with embolization are due to improved local delivery of chemotherapy, or the interruption of arterial blood supply. Up to now no chemotherapeutic agent has been reported to achieve effective as palliative treatment in GIST.

In our case, Epirubicin, recognized as one of the most active drugs in sarcomas, was delivered as IAHC. We decided to avoid embolizing agent, due to the heavy toxicities reported by other authors. We observed an evidence of disease progression in all three patients. In 1998, (pre-Imatinib era), we proposed Thalidomide (150 mg daily), a glutamic acid derivative with antiangiogenetic properties, as salvage treatment for our first patient (case 1). This patient obtained a disease stabilization for 6 months, with clinical improvement. Thalidomide in solid malignancies, is still under active investigation and seems interesting in tumors with hypervascular nodules.[10] In 2001, we adopted Imatinib (400 mg daily) as salvage therapy for the other cases (case 2 and 3). Patients obtained a partial response, lasting 18+ and 16 months. These cases suggest that IAHC is ineffective as palliative treatment in liver metastases from GIST, suggesting that the embolization, causing the interruption of arterial blood supply, remains the only intra-arterial palliative option. IAHC did not improve the local control of disease. Thalidomide, for the first time employed in GIST, showed interesting but minimal activity, that could be related to the characteristic hypervascular pattern of the disease. Further investigations of Thalidomide in this setting are warranted. In our experience, Imatinib has shown activity even in IAHC pretreated patients, confirming that no modifications induced by chemotherapy, even if at high local dosages as observed during IAHC, are able to induce any resistance to Imatinib. Demetri et al reported that about an half of 140 patients had been treated with systemic chemotherapy. They didn't report any difference in response rate after Imatinib, in both groups: pretreated patients and chemo-naïve patients.[11]

The application of Imatinib is really a major paradigm shift in cancer therapy-targeting the specific molecular abnormalities, crucial in the etiology of cancer. The first patient with GIST began a successful treatment with Imatinib in Finland, in February 2000.[11] The brilliant results in this first patient, along with the elegance of the scientific rationale, led to rapid expansion of this clinical translational research into large scale studies of Imatinib in GIST. Initially, 36 patients with unresectable or metastatic GIST were treated. Imatinib demonstrated efficacy and minimal toxicity, with a partial response rate of approximately 60%. This initial trial was then expanded to 145 patients treated with Imatinib, at a dose of 400 or 600 mg/day. The partial response rate was 59% and only 13% of patients progressed.[12] Confirmatory data have been reported by EORTC. In this study of 36 patients, the rate of disease progression was only 11%, with 69% of patients demonstrating disease response and 19% with stable disease.[13] These remarkable results are concordant with the larger study of U.S.-Finland collaboration.[12] The advent of Imatinib has revolutionized the clinical management of patients with primary and metastatic GIST. Further studies are warranted to better define the application of Imatinib in neoadjuvant, adjuvant and palliative setting of GIST.

REFERENCES


