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PET Scanning Evaluation of Response to Imatinib Mesylate Therapy in Gastrointestinal Stromal Tumor (GIST) Patients

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Abstract. *Background: Unresectable or metastatic gastrointestinal stromal tumors (GISTs) exhibit a dynamic clinical course, with no evidence of benefit from any standard cytotoxic chemotherapy and an inevitably fatal outcome. With the introduction of Imatinib, an oral drug able to inhibit the KIT receptor tyrosine kinase, new questions arise regarding our ability to monitor treatment response with conventional methods and optimally manage such patients on treatment with new agents. Materials and Methods: Herein we report two cases of patients with a history of GIST in treatment with Imatinib. Results: After 4 weeks from treatment start, CT scan evaluation demonstrated a massive increase in the size of metastatic lesions, but a confirmatory PET excluded, in both patients, the presence of any metabolic activity in the previously known metastatic sites. Imatinib therapy was continued with subjective clinical benefit for 12 further months before a PET scan-confirmed disease progression had occurred in one patient and is still ongoing after 15 months in the other. Conclusion: These cases open the obvious question of whether conventional imaging techniques are adequate to assess the response to Imatinib treatment in GIST patients.*

Gastrointestinal stromal tumors (GISTs) are soft tissue sarcomas arising from mesenchymal tissue in the gastrointestinal tract. They comprise 0.1%-3% of all GI cancers and 5% of all soft tissue sarcomas (1). GIST is defined as a c-kit-positive mesenchymal tumor, which preferably metastasises to the liver and peritoneum. Surgery has been the only effective treatment because GIST is resistant to radiation therapy and chemotherapy, but surgery alone is inadequate with an high percentage of relapse after primary resection (2). The most common symptoms are GI bleeding and abdominal pain, however, a high percentage of patients are asymptomatic.

Unresectable or metastatic GISTs have traditionally exhibited a dynamic clinical course, with no evidence of benefit from any standard cytotoxic chemotherapy and an inevitably fatal outcome (2,3).

The story of Imatinib in GIST represents a paradigm of molecular understanding leading to improved diagnosis and, ultimately, to an effective and novel targeted therapy. In fact Imatinib was found to inhibit the KIT receptor tyrosine kinase that is crucial to the pathogenesis of GIST (4). With the availability of a novel targeted therapy (imatinib mesylate) for a previously incurable disease (GIST) (4,5), new questions arise regarding our ability to monitor treatment response with conventional methods and optimally manage such patients on treatment with new smart molecules.

Materials and Methods

We have recently observed two patients affected by metastatic GIST in treatment with oral Imatinib at the standard dose of 400 mg/day, with similar evolution of the disease. A 63-year-old women (in November 1998) underwent to resection of retroperitoneal leyomiosarcoma. In March 2001 she had a resection of retroperitoneal relapse, but in October 2001 she developed liver metastasis (Figure 1a). In November 2001 we revised the histological examination, and the evaluation of CD 117 was positive (50%) (Figure 2).

Results

Before treatment start, the patient was afflicted by severe leg and sovrapubic oedema, and her Performance Status (PS) was 2. In December 2001, the patient started Imatinib at 400 mg/day and after only three weeks of treatment, she had a marked improvement of PS with a substantial

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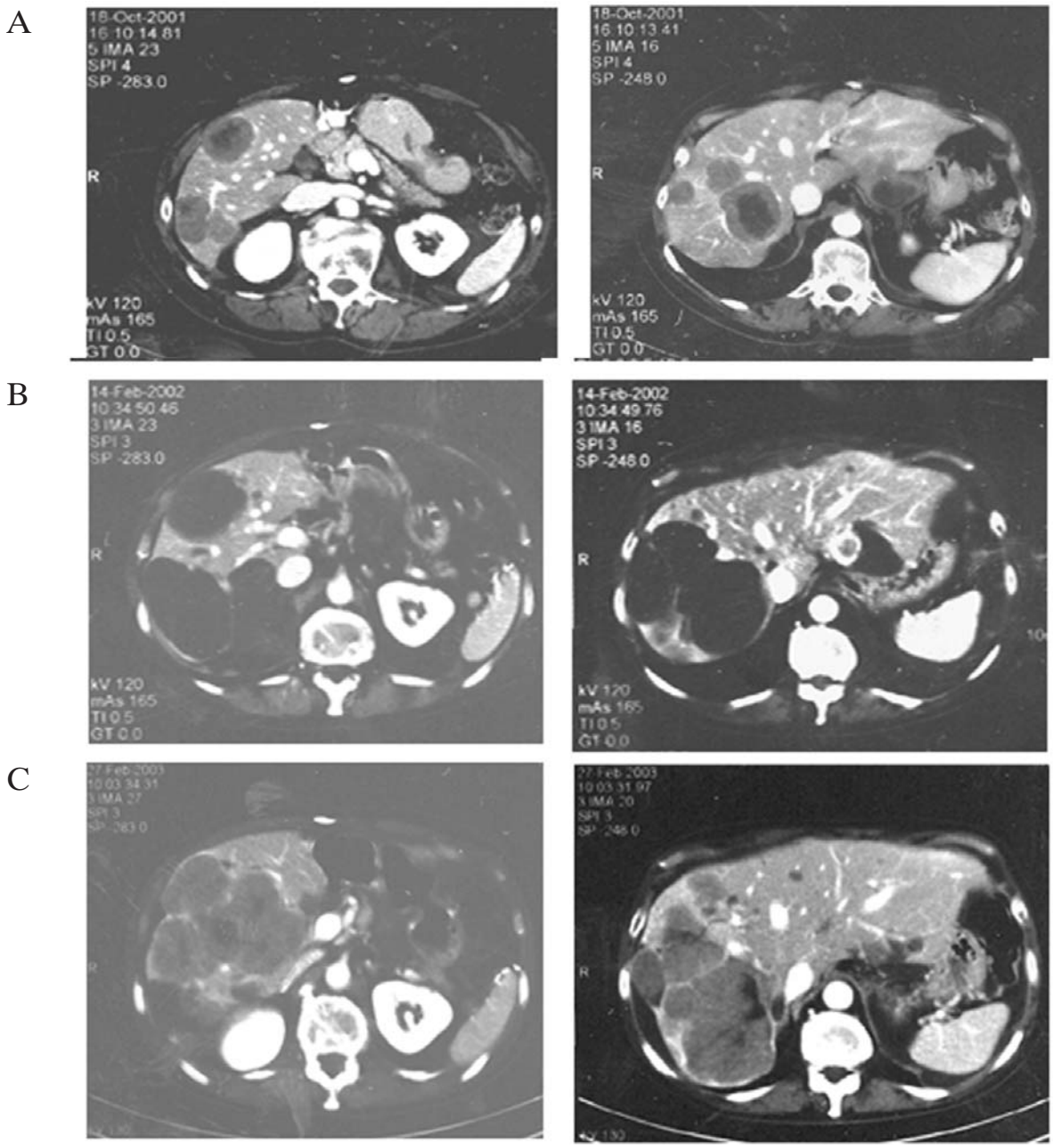

Figure 1. *CT scan assessment during treatment with Imatinib. A: Abdomen-pelvis CT scan performed before treatment start. B: After 10 weeks of treatment with oral Imatinib, 400 mg/day. C: Abdomen-pelvis CT scan performed after 14 months of treatment.*

reduction of symptoms. The only adverse event related to the drug was a mild perihorbital oedema (6).

Despite the marked symptom improvement observed within 3-4 weeks from treatment start, CT scan evaluation demonstrated a massive increase in the size of the metastatic lesions.(Figure 1b). Even though the appearance and density of the lesions had changed from solid to cystic, response to treatment should have been classified as progressive disease, according to standard WHO or RECIST criteria and should have led to treatment interruption or crossover, according to established clinical practice. However, preliminary evidence on the potential role of PET scanning in the evaluation of GIST response to Imatinib, suggested withholding of therapeutic decisions

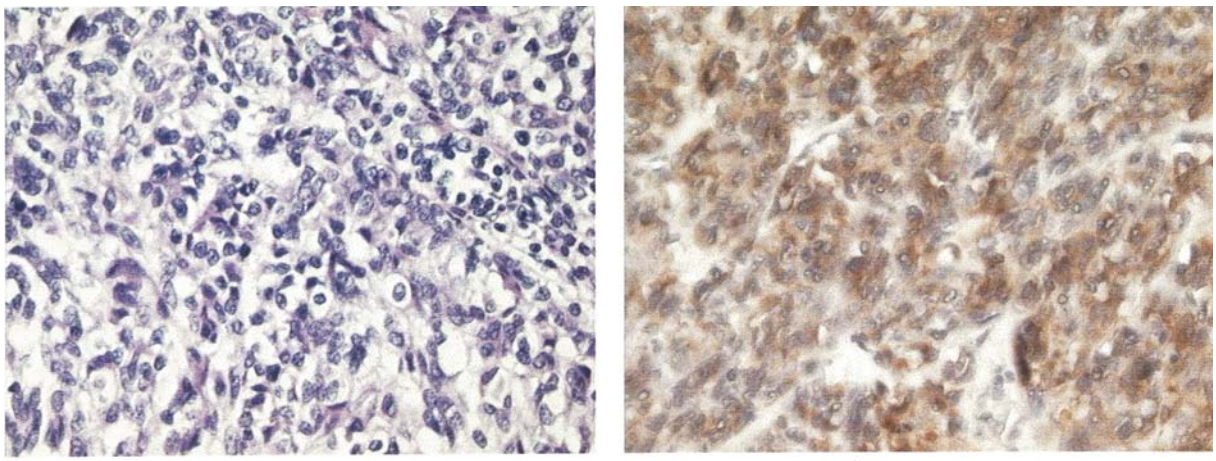

Figure 2. *Hematoxilyn/eosin staining of the primary tumor lesion (left panel, 40X) and immunohistochemical determination of CD 117 expression (right panel, 40X).*

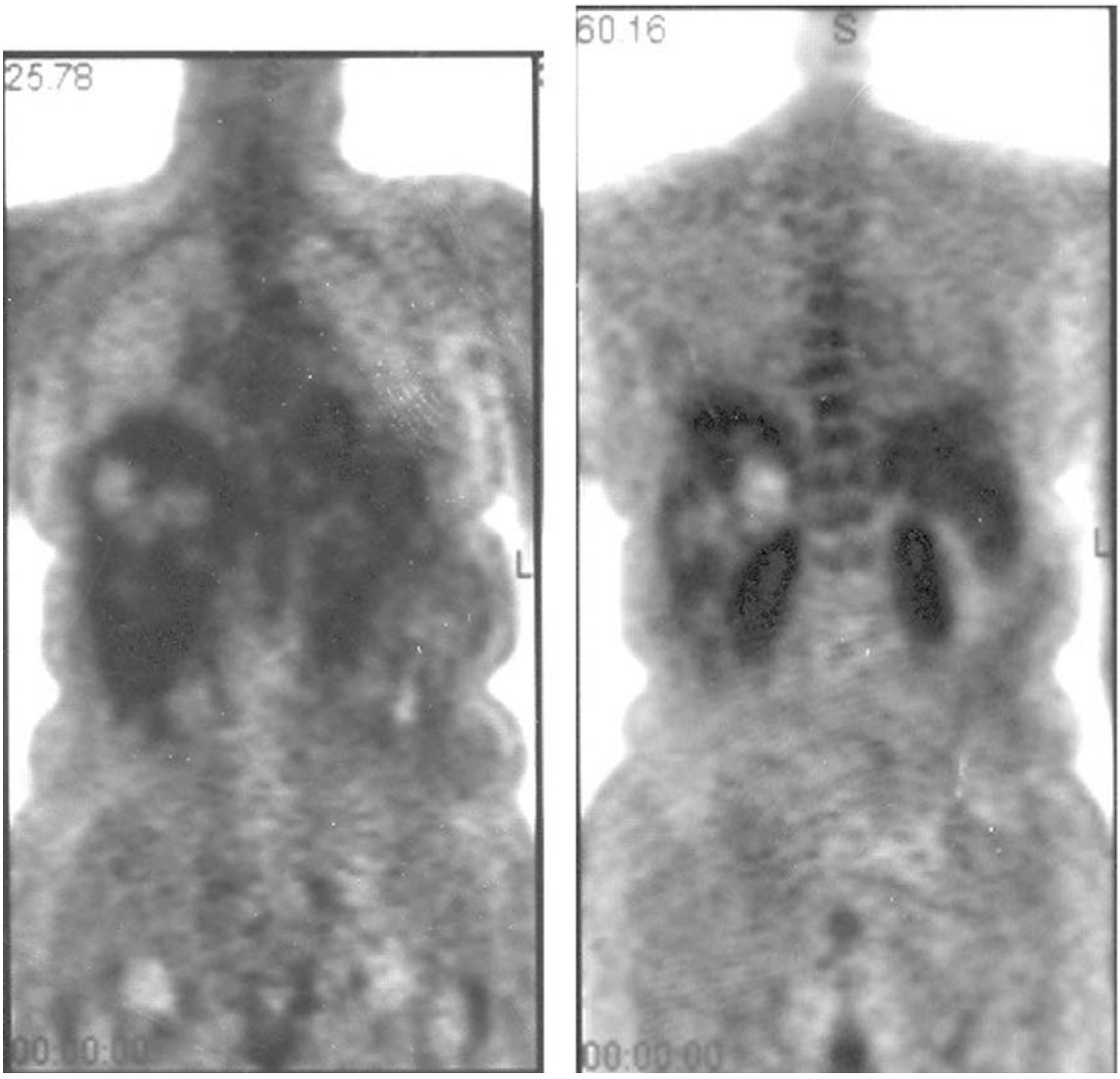

Figure 3. *PET assessment after 4 months (panel A) and after 13 months of treatment (panel B).*

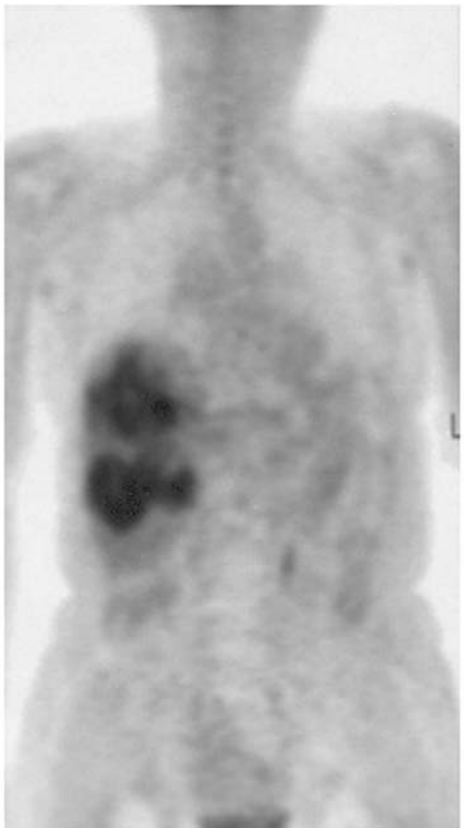

Figure 4. *PET scan performed after 14 months of treatment.*

and maintenance of both patients on imatinib therapy until a PET scan was obtained. The second patient, a 61 year-old man, had a similar course and the same strategy was employed, except for an increased dose (800 mg/day) after a second CT scan evaluation evidenced a further dimensional increase of liver lesion. In both patients, PET scan demonstrated the complete absence of metabolic activity in the previously known metastatic sites (Figure 3).

The response confirmed our clinical impressions: patients responded to therapy and there were no metastatic lesions in the sites evaluated positive by CT scan. Imatinib therapy was continued with subjective clinical benefit for a 12 further months before a PET scan confirmed disease progression (Figure 1c and Figure 4) had occurred in one patient and is still ongoing after 15 months in the other.

These cases have raised several questions: Is it still possible to evaluate the response to Imatinib only with CT scan? What should be the management of these big lesions be?

The two cases studied open the obvious question of whether conventional imaging techniques are adequate to assess response to Imatinib treatment in GIST patients.

Discussion

The control of cellular processes, such as cell growth, division and death, involves signal transduction, which commonly involves the transfer of phosphate from adenosine triphosphate (ATP) to tyrosine residues on substrate proteins, by tyrosine kinase enzymes. Activation of oncogenes coding for kinase proteins can lead to the production of kinases that are continually active in the absence of a normal stimulus, leading to increased cell proliferation and/or decreased apoptosis. A major focus of cancer research in recent years has been to identify oncogenic molecules and the signal transduction pathways in which they are involved, in order to develop specifically targeted drugs. One such drug is imatinib mesylate (imatinib, Glivec), an orally administered 2-phenylaminopyrimidine derivative that is a competitive inhibitor of the tyrosine kinases associated with platelet-derived growth factor (PDGF) receptors, and the KIT protein. Initial reports suggest an impressive role for (18) F-FDG PET in follow-up of therapy for these tumors. However, the role of (18) F-FDG PET *versus* that of CT has not been established.

In a recent series (7) early (8 days) complete or partial response by PET scanning predicted for a subsequent CT scan-confirmed response according to RECIST criteria in 10 out of 13 patients, while none of the 8 patients with stable or progressive disease on PET showed a subsequent response by CT scan. Regardless of concordance with CT scan results, PET response was clearly associated with a better progression-free survival (92% *versus* 12% at 1 year, $p=0.00107$).

A marked reduction in glucose uptake by FDG-PET occurs early during the treatment with Imatinib; in fact, as previously mentioned, FDG-PET responses 21-40 days after the beginning of treatment, are predictive of response to therapy. A decrease in the standard uptake value (SUV) of a tumor to < 2 during this period is predictive of a favorable outcome, whereas a SUV of >2 indicates a poor response or progression.

Another group compared the roles of (18)F-FDG PET and CT in staging and evaluation of early response to imatinib mesylate therapy in 54 recurrent or metastatic GIST. (8) The authors concluded that the performances of (18)F-FDG PET and CT are comparable in staging GISTs before initiation of imatinib mesylate therapy, however, (18)F-FDG PET is superior to CT in predicting early response to therapy. Therefore, despite financial and availiability restrictions, PET scanning could have an extremely important role in the evaluation of GIST patients treated with Imatinib mesylate, in whom tumor lysis is not usually observed despite metabolic tumor death, which leaves a residual mass that confuses anatomical readings. Metastatic lesions increasing in size during therapy should

be evaluated very carefully without overlooking the overall clinical picture and should not be construed to reflect progressive disease if the PET scan has become negative, because oedema around the tumor may occur and some lesions increase in apparent size while becoming more cystic. Appropriately designed clinical trials to prospectively assess the optimal management of patients with PET-negative residual tumor masses are eagerly awaited. Meanwhile, we believe it is reasonable to suggest that carefully selected patients with two or three dominant masses that have reached their maximal response to Imatinib with a negative PET scan be considered for surgery. This approach would, in turn, avoid the risk of intratumoral bleeding that is associated with tumor response during Imatinib treatment and may result in life-threatening haemorrhage (9).

Bleeding from the tumor site is not uncommon during the treatment of GISTs with Imatinib mesylate. It might represent an early reaction of highly vascularised tumor tissue to receptor blockade. Although often requiring emergency surgery, this is not necessarily a deleterious sign. Slow tumor regression and cystic tissue alteration may follow. A recent study showed that, using immunohistochemistry and consecutive resection specimens, the number of mitoses decreased significantly and MIB-1 as a marker of cell proliferation could no longer be detected (10).

In conclusion, informed clinical judgement based on all available data (CT scanning, PET scanning, clinical course, *etc.*) should be applied to the evaluation of tumor response to Imatinib therapy in GIST patients, in order to avoid prematurely withholding a potentially beneficial treatment.

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