Resistant GIST and redefining the role of F18 FDG PET

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ABSTRACT

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We herein explore the potential additional value of F18 FDG PET scans in the management of GIST, given the prompt metabolic response to targeted molecular therapeutic drug – Imatinib and newer drugs. Literature review on the molecular pathogenesis of the primary tumor and primary and secondary resistance to Imatinib therapy could pave the way for the potential use of F18 FDG PET scan in assessing and predicting early metabolic response, acquired resistance and prognostication in these tumors. This report highlights the various areas of clinical potential and the need for prospective studies to redefine and extend the role of F18 FDG PET scans in GIST.

Keywords: GIST, Imatinib, Targeted molecular drugs

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Manuscript text

Gastro intestinal stromal tumors (GIST) are rare tumors of the gastro intestinal tract with an annual incidence of about 10-20 cases per million. It is the most frequent mesenchymal malignancy of the gastrointestinal tract and liver and peritoneum are the most frequent metastatic sites. Surgery is the mainstay of treatment in patients with localized disease. These tumors (GISTs) are gaining the interest of researchers because of impressive metabolic response to the targeted molecular therapeutic drug Imatinib Mesylate.[1]

GIST cells express the CD 117 antigen (the KIT receptor tyrosine kinase molecule) in almost all the cases. KIT is the product of the KIT proto- oncogene. Activation of the KIT transmembrane receptor tyrosine kinase is mediated physiologically by stem cell factor, but several distinct mutations in the KIT gene can lead to a ligand independent and constitutive activation of the receptor. These mutations seem to be one of the underlying echanisms in the pathogenesis of GIST's. The site of mutation seems to correlate with response to Imatinib.[6]

The most common primary mutation in GIST is an in frame deletion in exon 11, which leads to the gain of function alteration in the juxta membranous part of the receptor tyrosine kinase.[7] In 30% of GIST, instead of the abovementioned defect, a mutation in exon 9 or 13 of KIT or mutation in a different tyrosine kinase receptor namely platelet derived growth factor Alfa, have been found.[8,9]

Hence most gastrointestinal stromal tumors (GIST) have an activating mutation in either KIT or PDGFRA. Imatinib is a selective tyrosine kinase inhibitor of KIT and achieves a partial response or stable disease in about 80% of patients with metastatic GIST and some other malignant diseases.[1]

This scenario can be thought of as "oncogenic addiction" and is one of the major reasons why some GISTs respond significantly to therapies that target these mutant receptors. In addition to mutations in c-KIT or PDGFR-alpha, genomic alterations contribute to disease progression. Moreover, GISTs that harbor different c-KIT or PDGFR-alpha mutations have different molecular signatures at the level of gene expression, which further contributes to the complexity of GIST biology and variable responses to treatment.

Initial response rates are high, but disease progresses after a variable period of time in most patients. This is because some patients with GIST develop resistance to Imatinib during chronic therapy, probably due to mutations in the homologous kinase platelet derived growth factor receptor alpha (PDGFRA), and the most common of these mutations is resistant to Imatinib in vitro. There were no secondary mutations in KIT or PDGFRA in the nonresistant or primary resistance groups. In contrast, secondary mutations were found in 7 of 15 (46%) patients with acquired resistance, each

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of whom had a primary mutation in KIT exon 11.

Studies have shown the high frequency of KIT/PDGFRA kinase domain mutations in patients with secondary resistance and defines genomic amplification of KIT / PDGFRA as an alternative cause of resistance to the drug. In a subset of patients, cancer cells lost their dependence on the targeted tyrosine kinase. Thus reactivation of KIT is the most important mechanism of secondary resistance, with half of these cases showing KIT mutation.

Another mutation described at exon 17, encoding for the kinase domain, causes structural alteration preventing binding of Imatinib. This mutation is common in familial GIST and rarely present in sporadic GIST's. Mutations in exon 13 also affect the structure of the kinase domain rendering Imatinib ineffective[10,11]

Studies suggest that there are 289 reported PDGFRA-mutant GISTs, of which 181 (62.6%) had the Imatinib-resistant substitution D842V. However their findings suggest that more than one third of GISTs with PDGFRA mutations may respond to Imatinib and that mutation screening may be helpful in the management of these tumors. The responsiveness of mutant PDGFRA-positive GIST to Imatinib depends on the location of the PDGFRAmutation; for example, the V561D juxtamembrane domain mutation is more sensitive to Imatinib than the D842V kinase domain mutation. A, comparison on the effects of 3 tyrosine kinase inhibitors, PKC412, nilotinib, and Imatinib, on 2 GIST-related PDGFRA mutants, V561D and D842V, which possess differential sensitivity to Imatinib showed that PKC412 potently inhibited the V561DPDGFRA mutant in vitro and the D842V-PDGFRA mutant in vitro and in vivo. Both Imatinib and nilotinib displayed potent activity in vitro against the V561D-PDGFRA mutant but were significantly less efficacious against D842V-PDGFRA. However, when combined with either Imatinib or PKC412, nilotinib showed no evidence for antagonism and acted in a cooperative fashion against D842V-PDGFRA.

The discovery of these newer drugs and documentation of the mechanisms of resistance primary or secondary, could pave the way for utilizing F18 FDG PET in a totally different way than what is current practice. One such area is early response assessment of GIST to therapy, as it has been reported that FDG PET shows metabolic response in GIST as early as 24hours after starting therapy. A signaling switch-off in metabolic activity that early, which precedes by a long time what can be seen on CT or MRI, would be a very valuable tool in treatment planning and patient management.

If an adequate response is not seen early in therapy, alternative drugs alone or in combination with Imatinib can be substituted, thus avoiding unnecessary side effects and cost of therapy. This would of course, require prospective trials to establish normal patterns of early response in GIST and corroborate it with long-term disease free survival and development of resistance to chronic therapy. As of now, FDG PET is used to assess tumor response to Imatinib after a period of about 2 months, as it has been documented that a good metabolic response at this time point confers a longer disease free survival in patients. However an earlier response evaluation within 24 hours or 1 week, if standardized would enable alterations in therapy expeditely.

This would also raise a question as to the utility of FDG PET scan in long term monitoring of these patients; the issue being whether any recurrence of tumor or acquired resistance in patients on chronic Imatinib, would pick up FDG. Ideally FDG being a glucose analogue should go to any cell with a heightened glycolytic activity, irrespective of the site of their mutation. Case reports on tumors with acquired resistance to Imatinib due to an additional mutation at exon 17 and 13, have been reported to be FDG avid. On the other hand there are reports of Imatinib resistant mutant GIST to display only low grade FDG concentration on serial PET scans, while deteriorating clinically and on CT scan. This has been explained on the basis of Imatinib successfully inhibiting phoshorylation or F18 FDG uptake while being unable to stop tumor progression and cell proliferation.[6] As both the cases in this report had an additional mutation in exon 17, prospective analysis and laboratory studies of response to Imatinib in cells harboring KIT mutations on exon17; should provide useful insights. This raises important issues in therapeutic monitoring of GIST patients treated with KIT inhibitors.

As the issue of developing resistance in the long term would be one of the major factors affecting disease free survival in these patients, the important aspect of being able to prognosticate or predict a worse outcome becomes paramount.

Gastrointestinal stromal tumors (GISTs) have a wide spectrum of biologic behavior ranging from benign to malignant. Risk grading based on tumor size, grade and mitotic counts has been proposed in an effort to predict the adverse outcome of GIST in the literature so far. Recent molecular studies have reported the prognostic

values of several parameters, including alteration of cell-cycle regulators such as. Ki-67 LI, alteration of G2-M regulators, such as cyclin A, cyclin B1, and cdc2, as useful markers for predicting aggressive behavior and play an important role, at least in part, in the cell proliferation of GIST. So the question whether semi quantitative analyses using SUV's on F18 FDG PET can be used as asurrogate marker for cell proliferation at the time of initial diagnosis is of utmost importance and needs well-controlled studies before a definite answer can be given. Another potential marker for aggressiveness is doing a dual time point FDG PET SUV analysis and correlating the progressive increase in glucose uptake with tumor grade. There are reports of similar studies pertaining to other malignancies such as breast cancer and this is a potential area of development.

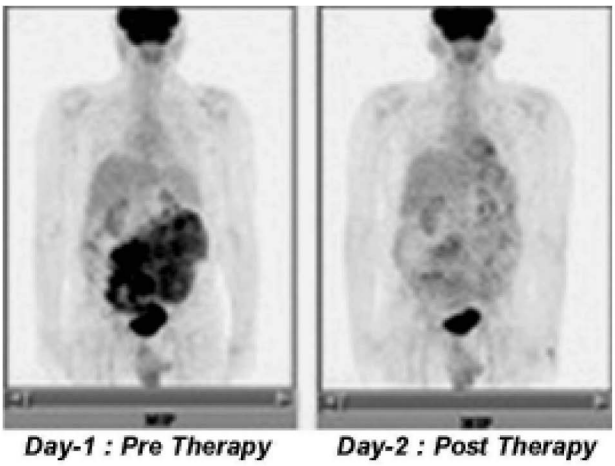

Figure 1. **FDG PET image**

The two whole body FDG PET image is of a patient with histologically proven GIST, the first one is a baseline scan and the other one is 24 hours later with a single dose of ImatinibMesylate oral tablet. There is significant decrease in metabolic uptake (almost 85 % decrease) with a single dose, suggesting good treatment response and long term disease free survival.

END NOTE

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