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Use of positron emission tomography in oncology and its potential role to assess response to imatinib mesylate therapy in gastrointestinal stromal tumors (GISTs)

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Abstract

The reliability of established anatomical imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), is compromised in following response to certain types of treatment if metabolic improvement occurs before morphologic change is apparent. Thus, traditional imaging techniques cannot discriminate early tumor response because they are based on purely visual structural assessments. Recently, the use of positron emission tomography (PET), most commonly employing the radiotracer ^{18}F-fluoro-2-deoxy-D-glucose (FDG), has been shown to improve the assessment of tumor behavior by highlighting early functional changes in tumor glucose metabolism that appear to correlate closely with metabolic tumor response to imatinib mesylate. Like CT and MRI, PET can identify an abnormal mass; its improvement over these techniques lies in its ability to differentiate active tumor from necrosing tissue, malignant from benign tissue, and recurrent tumor from scar tissue. Understanding and using this tool should improve our ability to accurately follow response in GIST patients treated with imatinib mesylate, and permit this new therapeutic approach to be used optimally with accurate follow-up assessments and informed therapeutic decision-making.

Keywords: Positron emission tomography (PET); ^{18}F-fluoro-2-deoxy-D-glucose (FDG); Gastrointestinal stromal tumor (GIST)

1. Introduction

Our ability to assess the activity of imatinib mesylate (Glivec®, formerly STI571, Novartis Pharma AG, Basel, Switzerland) in gastrointestinal stromal tumors (GIST) is complicated by the histologic character of the therapeutic response. Traditional anatomical imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), provide detailed information about the location, size and progression of tumors as well as the involvement of adjacent tissue and neurovascular invasion. Although these tools can identify an unusual mass and define its location and extent, they cannot alone differentiate malignant from benign tissue, or recurrent tumor from scar tissue. The distinction is further compromised in GIST treated with imatinib mesylate, where significant metabolic tumor response seems to occur before morphologic change is apparent and tumor cellularity can persist despite histologic evidence of degeneration and fibrosis [1]. Therefore, it is important to select a method that provides early and accurate estimation of therapeutic response in patients with GIST.

More than 70 years ago, Warburg first observed that tumor cells exhibit increased glucose metabolism [2,3]. It has since been established that increased glycolysis is among the key metabolic alterations marking the transformation from normal to malignant cells in nearly all tumor types [4,5]. This metabolic feature of tumor cell biology suggested a model system in which to apply positron emission tomography (PET), which is the most sensitive method for quantifying molecular pathways in

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vivo [6]. PET uses radiotracers that consist of molecules that mimic endogenous compounds labeled with positron emitters, which can then be introduced into a human, incorporated into molecular systems and visualized tomographically. The information derived from this technique provides information related to the behavior of the radiotracer within the patient's biologic system, revealing normal as well as abnormal behavior. The most commonly used radiotracer is ^{18}F-fluoro-2-deoxy-D-glucose (FDG), a glucose analog that readily enters the early steps of glucose metabolism, but does not complete the glycolytic pathway and remains trapped within the cell. As a result, FDG accumulation within the cell is a measure of glucose uptake, and it can be used in oncology to differentiate between normal glucose metabolism and the enhanced glycolysis of tumors. Therefore, this imaging technique provides a functional assessment of tumor behavior that can highlight early changes in tumor glucose metabolism that potentially correlate with tumor response to imatinib mesylate.

The focus of this paper is on the technique of PET, its relevance and usefulness in oncology, and its anticipated special value in the management of GIST patients receiving imatinib mesylate therapy.

2. Historical perspective on use of PET in oncology

The development and clinical application of imaging technologies, such as CT, MRI and ultrasonography, has greatly advanced our ability to detect, measure and characterize tumors, contributing to increasing success in diagnosis and treatment planning in oncology. However, these techniques have shortcomings as diagnostic tools in oncology, i.e., the anatomic/morphologic information they provide fails to clearly distinguish malignant from benign tissue, tumor from scar tissue, and poorly differentiates the outer limits and distribution of active and metastatic tumor growth [7].

2.1. PET: the technique

PET provides a functional and metabolic complement to the anatomic imaging tools. PET utilizes radiolabeled organic compounds that mimic certain physiologic and pathophysiologic processes. The radionuclides used in PET decay by positron emission. An emitted positron will travel approximately 1 or 2 mm in human tissue before undergoing an annihilation reaction with an electron. In this reaction, both the positron and the electron are destroyed, and two high-energy gamma rays travelling in opposite directions are produced. These gamma rays may be detected by a PET scanner, and the resulting data can be tomographically reconstructed to reveal the distribution of radiotracer within the subject. A nuclear medicine physician can use these data to describe the specific metabolic activity related to the biologic path of the radiotracer; these findings can be valuable in medical assessment and treatment planning.

PET scanners provide accurate in vivo functional image maps at sub-picomolar radiotracer concentrations, that is 5 to 6 orders of magnitude lower than the tracer concentrations required for functional MRI [6]. Although PET provides poorer anatomic resolution than the conventional imaging techniques, the information it provides is crucial to understanding the status, metabolic activity and molecular pathways of cancer. For instance, PET enables us to diagnose and characterize tumors, as well as differentiate benign from malignant masses, on the basis of physiologic parameters such as glycolytic activity, protein synthesis, or specific receptor concentrations [8]. In circumstances where the poorer anatomic definition provided by PET renders interpretation more difficult, fusing PET data with either CT or MRI scans can provide images richer in information than either functional or anatomic images on their own.

2.2. FDG PET — the rationale

The underlying rationale for FDG PET depiction of malignancy is the increased rate of anaerobic glycolysis that occurs with tumor cell dedifferentiation [7]. Chemical similarities between FDG and glucose allow it to be transported into the cell by endothelial glucose transporters at roughly the same rate as glucose; within the cell it is rapidly phosphorylated by intracellular hexokinase, yielding FDG-6-phosphate. This radioactive metabolite of the original tracer accumulates in the cell because FDG-6-phosphate, unlike glucose-6-phosphate, is a poor substrate for the subsequent enzymatic systems.

If sequential (dynamic) PET scans are acquired following tracer injection, together with direct measurements of arterial radiotracer concentration over time, the uptake profile of radiotracer over time may be determined. These data may be used as input to a mathematical model (known as a compartmental model) to derive the absolute local rate of glucose metabolism in units of mmol/min/g. However, this process is demanding, invasive and cannot be applied in the context of whole-body imaging. Static imaging, in which patients are imaged at a time when significant tracer accumulation has occurred (usually 45 min to 1 hour post-injection), provides an approximate but clinically useful measure of local glucose metabolism that is much more practical for routine use (Fig. 1). The development of the whole-body PET scanner permits imaging a patient in this manner from head to foot, or any portion in between.

The FDG PET scan has been validated for measuring glucose metabolism in the brain and the myocardium, where there are high levels of hexokinase and low glucose-6-phosphatase activity [9–11]. The rationale for this technique in other systems or tissues that utilize glucose led investigators to examine its role in a variety of tumors, with consistent success: several investigators have reported

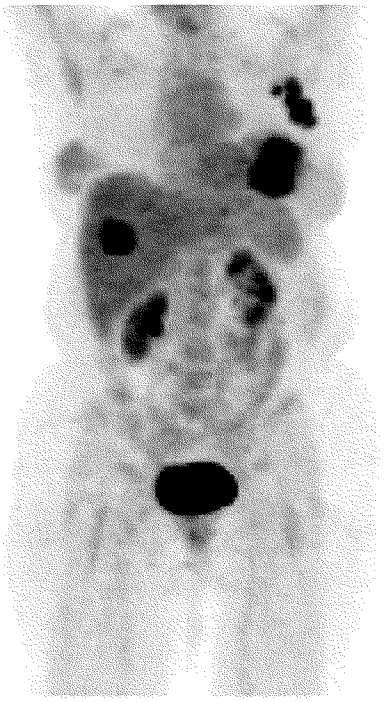

Fig. 1. FDG-PET scan obtained in a patient with breast cancer demonstrating abnormal FDG uptake within the primary in the left breast, metastatic adenopathy in the left axilla and a liver metastasis.

findings of elevated glucose transport, increased hexokinase levels and low glucose-6-phosphatase levels in a range of tumor types, including breast, lung, head and neck, musculoskeletal and sarcomas [11–15]. Today, it is considered the most reliable test to distinguish malignant tissue from benign tissue and recurrent tumor from scarring and to diagnose and stage a variety of neoplasms, including lung cancer, lymphoma, melanoma, breast cancer, gastrointestinal cancers, head and neck cancers and musculoskeletal cancers.

2.3. Assessing response to treatment

Although still in the early stages of investigation, several scientists have explored the use of PET to assess the efficacy of treatment. In lung cancer, several reports have documented a correlation between decreased uptake on PET following chemotherapy and more favorable outcome [16–19]. In head and neck cancer, FDG PET has been shown to accurately evaluate response to therapy and to predict short-term outcome at both primary tumor sites and metastatic lymph nodes [20–23]. The limited data from breast cancer trials also suggest that a rapid decrease in FDG uptake correlates with the clinical efficacy of therapy [24–27]. Based on these successes, it seemed logical to extend the concept to test PET as a tool to follow treatment response to a molecular therapy like imatinib mesylate in GIST.

3. PET — a clinical trial tool for assessing response to imatinib mesylate

GISTs are the most common mesenchymal tumors of the stomach and proximal small intestine that only recently have been clearly differentiated from other gastrointestinal neoplasms using molecular biology and cytogenetics. In the 1960s, GISTs were classified as smooth muscle tumors, clinically indistinguishable from leiomyosarcomas, leiomyomas and schwannomas [28]. In the late 1990s, however, a report linking GIST to a specific gain-of-function mutation in the c-Kit gene and overexpression of the receptor tyrosine kinase [29] provided the tools to differentiate GIST from other gastrointestinal mesenchymal tumors. Today, GIST is recognized as a clinically and pathogenetically distinct stromal tumor defined by constitutive activation of the c-kit tyrosine kinase [30] and identified histopathologically by expression of CD34 and/or CD117 proteins [31–35].

Many approaches to the management of inoperable, malignant GIST have been attempted, with little success. Systemic chemotherapy and local radiotherapy have proved ineffective [36–38] and the likelihood of distant metastases has impeded the success of surgical resection [39]. The identification of a molecular target to prevent the pathogenesis of GIST and, perhaps more importantly, the development of a compound like imatinib mesylate with the potential to intervene at the relevant molecular site [40,41] provides hope for patients with this heretofore virtually incurable disease.

Detecting response to a cytostatic drug is more complicated than detecting response to a cytotoxic drug, whose clinical efficacy is correlated with the destruction of cells and a decrease in tumor size. A cytostatic drug functions at a molecular level to halt the neoplastic process, but does not necessarily have a direct effect on lesion size. Thus, it is unclear whether tumor response will be visible on anatomic imaging scans such as CT or MRI, particularly in the early treatment period. With this in mind, it was considered a rational approach to include PET scans with FDG in the treatment follow-up to imatinib mesylate in GIST.

To date, several trials of imatinib therapy for GIST have employed FDG PET scanning to assess response to therapy, with promising early results. The GIST Collaborative PET Study Group reported preliminary results at the 2001 Annual Meeting of the American Society for Clinical Oncology (ASCO), noting that PET revealed treatment responses as early as 24 hours after initiation of therapy and provided information regarding extent of disease, tumor metabolism and resistance to imatinib mesylate in patients with advanced GIST [42]. Fig. 2a,b shows a patient with GIST prior to imatinib therapy demonstrating that the tumor is glycolytically active, and 1 month following initiation of therapy when there is no evidence of persisting glycolytically active tumor. Blanke and colleagues also

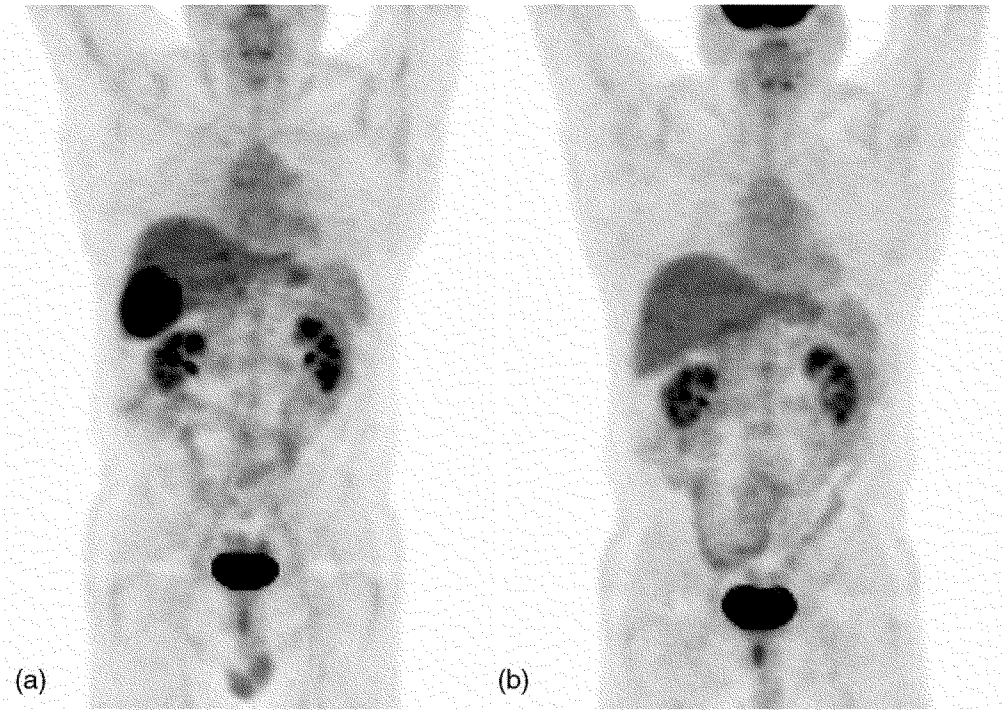

Fig. 2. FDG-PET scans obtained in a patient with GIST prior to (a) and 1 month following imatinib mesylate therapy (b) demonstrating the resolution of the abnormal uptake seen at baseline in the liver.

reported at ASCO that in their study of 36 patients with metastatic or unresectable GIST, CT determined partial responses (54%) or stable disease (34%) associated with imatinib therapy, which correlated closely with a finding of $\geq$50% decrease in FDG uptake on PET scan in 89% of patients [43]. The European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group also reported that dramatic reductions in FDG uptake was observed in 15 of 16 documented GIST patients treated with imatinib mesylate, which they reported to predict current or impending clinical improvement of disease [44].

4. Other uses for PET

The specificity of PET and the detailed functional information it provides are useful in a variety of clinical oncology settings. PET has proved to be invaluable in the diagnosis of many cancers, including soft tissue and musculoskeletal carcinomas [7,8,45–47]. Other investigators have shown that FDG accumulation can be correlated with tumor grade [48,49]. The specific information provided by PET, including malignant metabolic activity, degree of aberrant metabolism and nature of the lesion, provide important details to be considered during treatment selection and surgical planning.

FDG PET data can distinguish metabolically active tissue from necrotic or benign tissue. It can also differentiate tumor tissue from changes related to edema, inflammation or scarring. Griffeth and colleagues used PET to identify the malignant tissue within five large nonhomogeneous soft tissue masses, which they then used to guide surgical biopsy boundaries [7]. This allowed for more conservative surgical procedures than might otherwise have been possible, thereby reducing morbidity. They also noted that in five lesions determined benign on PET, results seen on CT and MRI were equivocal and might have instigated aggressive intervention rather than the more appropriate "watch and see" approach.

PET is especially useful for following patients after treatment for soft-tissue lesions. After surgery or chemo- or radiotherapy, tumor tissue undergoes anatomic disruption and distortion of tissue planes, making it difficult to read with anatomic imaging tools. FDG PET can accurately distinguish benign tissue from disease recurrence at these sites, focusing subsequent intervention in the most effective and conservative direction. This should have an important benefit for GIST patients treated with imatinib mesylate, in whom tumor lysis has not been observed despite metabolic tumor death, leaving a residual mass that confounds anatomical readings [1].

FDG PET can also identify regional or even distant metastases. The most common site for GIST metastases is the liver, with less frequent evidence of dissemination within the peritoneal cavity or local relapse [50]. These metastases are well within the landscape of the typical PET imaging range for GIST, which is the base of the skull to the proximal thighs.

5. General discussion

PET is the most sensitive and specific tool for imaging molecular pathways in humans. Using positron-emitting radionuclides to label organic molecules that are absorbed into physiologic systems, PET can image molecular interactions and pathways, providing detailed information about normal and/or abnormal metabolic and cytogenetic functions. Within the human system, the positrons emitted by the radionuclides annihilate with electrons to generate gamma radiation that is detected by the PET scanner. The data acquired by the scanner are then reconstructed tomographically, yielding an image of the radiotracer concentration within the patient. The spatial resolution of this technique is lower than that of CT or MRI, but the metabolic information it provides is unique.

The functional information provided by FDG PET can be used to clearly distinguish between benign and malignant tumors. The metabolic assessment performed by FDG PET also allows us to distinguish necrotic tissue from recurrent disease, which is particularly useful at sites with scar tissue or tissue otherwise altered by previous intervention. The availability of whole-body FDG PET has further increased the utility and value of this technique, allowing for identification and diagnosis of metastatic disease at distant sites throughout the body.

Our decision to include PET evaluation in the clinical trials examining imatinib mesylate therapy in GIST was particularly fortuitous; we did not necessarily anticipate the striking early metabolic response to imatinib mesylate that were noted in the clinical trials to date. Significant decreases in FDG absorption have been seen as early as 24 hours after initiation of therapy, and may possibly reflect changes in tumor metabolism predictive of antineoplastic response. This is an area of ongoing research. These readings almost certainly could not have been measured on CT or MRI at that early stage and, in fact, may not have been anatomically imaged for many weeks. This might have led to the conclusion that imatinib mesylate was ineffective, or to the use of more aggressive alternative or combination therapies to achieve a greater morphologic tumor response. This misreading of anatomic imaging data would have been further confounded by the later finding in clinical trials that GIST metabolic death is not necessarily accompanied by a lytic cellular response, making CT and MRI readings more difficult to discriminate. The PET metabolic readings helped in recognizing the molecular treatment response in this case.

The concept of using FDG PET to assess treatment response in oncology is not new and has been reported to provide useful information in lung, head and neck, breast cancers and other tumors. Although the data are still young, FDG PET has been found to be a reliable measure of many clinical parameters, and is able to identify subclinical treatment responses, predict short-term outcome, later antineoplastic response and disease prognosis. Our experience using FDG PET to follow imatinib mesylate therapy in GIST suggests that there is a relationship between FDG PET findings and disease state and may provide further confirmation that FDG PET is a reliable tool to diagnose, stage and assess therapeutic response.

In summary, FDG PET is the best technique available to assess the functional viability of tumor cells noninvasively and may become an essential tool in evaluating the molecular response to therapy. PET is becoming an invaluable tool combined with other imaging techniques for the full management program — from diagnosis to treatment planning and assessment of therapeutic response — in cancer patients.

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