PET and PET/CT in gastrointestinal stromal tumours: the unanswered questions and the potential newer applications

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The scientific evidence over the last decade has demonstrated the revolutionary impact of FDG PET as an excellent molecular imaging tool for evaluating early therapeutic response of gastrointestinal stromal tumours (GIST) to imatinib mesylate [1]. By now, it is quite evident that the early response of GIST to imatinib therapy cannot be reliably monitored by the World Health Organization (WHO) criteria, Response Evaluation Criteria in Solid Tumors (RECIST) or the Southwest Oncology Group (SWOG) criteria for assessing treatment response that are solely based upon changes in the tumour size measured by morphological imaging modalities. The results have now been well validated in multiple head-to-head prospective studies with sufficient statistical strength [2–13] that have convincingly proven that FDG PET or PET/CT imaging has been the imaging modality of choice to assess metabolic activity in this group of tumours. Comparing PET activity before and after the start of tyrosine kinase inhibitors provides critical information in identifying active disease and for the assessment of the response to drug treatment. While this has been the major thrust and the frequently highlighted aspect of FDG PET imaging in the management of GISTs, there are other practical issues where this powerful imaging modality can be of great help, and answering these clinical concerns is likely to further enhance the prospects of PET-guided personalized medicine in GIST.

Tailoring and selecting the optimal treatment dose is of great benefit in minimizing the toxic effects of this therapy.

The relatively common dose-limiting adverse effects of imatinib as observed in the phase I studies [14] include oedema, nausea, vomiting, rash and musculoskeletal pain. Though generally well tolerated they are particularly common and are of concern for patients who are of smaller size with cachexia, poor performance status and a large disease burden. Many of them quickly develop oedema or a fluid compartmentalization during imatinib therapy. Hence this has a geographic relevance and is of more concern in developing countries than in their Western counterparts. Presently, a starting dose of 400 mg daily is considered appropriate for most patients with GIST, but patients with an exon 9 mutation of the KIT gene usually require a higher dose. A dose increase is considered by the oncologists when they fail to respond. The results of two large phase III trials (EORTC/ISG/AGITG 62005 and SWOG/CALGB/NCI-C/ECOG/ICAS S0033) have demonstrated similar responses for imatinib doses of 400 mg/day versus 800 mg/day when mutation status is not considered [15]. However, in both trials, dose reductions due to side effects were much more common in the 800-mg groups than in the 400-mg groups [15]. Severe congestive cardiac failure is another uncommon but recognized side effect of imatinib and it is predicted that cardiotoxicity could be facilitated by the presence of relevant comorbidities such as pre-existing cardiovascular disease or renal failure [16]. The incidence, natural history and risk factors for developing cardiotoxicity is not clearly defined in the clinical context [17]. Preclinical studies indicate that imatinib and sunitinib may be directly toxic to cardiac myocytes and it is described to be more common and severe with sunitinib [17]. All these imply that starting of therapy at lower doses of these drugs may be considered in appropriate cases with a goal of escalating the dose further when required. Molecular imaging with FDG PET by its ability to document early response can play a pivotal role to tailor and

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optimize the dose of imatinib or sunitinib and should be employed more frequently to define the most appropriate dose in an individual. In our experience, low-dose imatinib (200 mg daily) administration in case of documented side effects with the standard 400 mg dose can be quite effective in disease suppression as observed by metabolic FDG PET imaging and should be considered in such settings.

The clinical and pathological criteria to differentiate benign from malignant GIST are not well established and are at times notoriously difficult [18]. Tumour size and mitotic activity are commonly considered major discriminants predictive of biological behaviour. Tumours with size >5 cm and mitotic activity counts > 5/50 high power field (HPF) are considered to be malignant and those with size less than 5 cm and mitotic activity counts <5/50 HPF are likely to be benign. This, however, leaves a grey area in the separation of benign and malignant tumours and the tumour biology depends on several other factors [20]. Comparative studies of KIT-mutant, PDGFRA-mutant and wild-type GISTs indicate that there are important differences between these groups of tumours and hence a molecular-based classification of GIST appears more appropriate rather than the aforementioned two factors alone [19]. Furthermore, the significant amount of necrosis that is commonly encountered in these tumours can lead to sampling error during anatomical imaging-guided biopsy and yield falsely low mitotic count in the biopsied specimen. We have observed a similar phenomenon in our prospective series [1]. It has been observed that among mitotically inactive tumours there is a small percentage that later metastasize, illustrating that a low mitotic count does not rule out the possibility of malignant behaviour [20]. FDG PET by its ability to measure metabolism can play an important role in characterizing the tumour phenotype by distinguishing metabolically active malignant GISTs from their benign counterparts and also guiding the appropriate site of biopsy. Kamiyama et al. [21] investigated ten patients to explore the usefulness of FDG PET in predicting the malignant potential, where FDG uptake and malignant potential (Ki-67 index and mitotic index) of gastric GISTs had a significant correlation. Similar observations have been made by Yamada et al. [22] in 21 patients and the results of both these studies provide impetus for yet another promising clinical application of this molecular imaging technique in characterizing and grading these tumours. It will be also worthwhile to study whether any difference in FDG uptake pattern exists amongst the various molecular subtypes with differing mutations.

The “metabolic switch-on” in FDG PET imaging in a compliant patient can indicate secondary resistance to imatinib related to newly acquired second mutations, and the role of this imaging modality in the follow-up of the patients who had shown an initial response to this therapy has been recently underscored by various authors [1, 23].

The secondary drug resistance can present in the form of an otherwise responding tumour that starts to grow or as appearance of new metastases. It is presumable that metabolic imaging with FDG PET will be able to detect secondary drug resistance ahead of other anatomical imaging modalities. As more drug options become available, the use of FDG PET imaging for this purpose will hopefully become more common in order to select the best drugs at the earliest opportunity in such settings. We have observed similar FDG PET imaging features in disease relapse in patients who were non-compliant and discontinued treatment themselves due to financial constraints [1], which can be encountered in patients of poor socio-economic status. This is related to the cytostatic nature of the therapy with the small molecule tyrosine kinase inhibitors such as imatinib and sunitinib.

Another important observation of recent times has been the rebound of tumour metabolic activity within a few days after stopping imatinib treatment in imatinib-resistant GIST patients, who were being contemplated to be started on multitargeted receptor tyrosine kinase inhibitor sunitinib malate [24]. This observation suggests that a fraction of the tumour cell population continues to be responsive to imatinib in these patients, whereas the secondary resistance and disease progression occur in the resistant clone due to a mutation that is resistant to imatinib [23, 24]. The finding can be related to the fact that substantial intra- and interlesional heterogeneity of resistance mutations and gene amplification exist in patients with clinically progressing GIST [25]. This observation is noteworthy as it provides significant insight into this condition and can thereby provide the basis for therapeutic approaches that would include the cocktails of drugs in treating these patients with secondary resistance to imatinib. Furthermore, it is emphasized that the advantages of the combination regimen include not only the opportunity to maximize initial clinical response, but also the possibility to reduce the incidence of developing secondary resistance, as compared to a monotherapy regimen. Till date, this approach is a relatively unexplored area in GIST research and requires examination in further prospective studies. While certainly an attractive option, the principle of a “cocktail” approach with combinations of drugs is relatively complex and requires defining the correct doses of each drug to minimize the related adverse effects on normal cells. Here again, FDG PET imaging results would prove crucial for optimizing the dose of each drug on a case to case basis and thereby minimizing the likelihood of synergistic side effects related to combination therapy.

An important aspect of GISTs is their association with synchronous or metachronous malignancies, the list of which continues to expand [1]. PET/CT, being a whole-body tomographic technique, can be effectively exploited to this

end for identification of other malignancies with high sensitivity [1].

Platelet-derived growth factor receptor α (PDGFRA) mutations have also been observed in GISTs and it is suggested that mutational activation of KIT or PDGFRA are mutually exclusive, represent two different alternative oncogenic events and show differing clinical characteristics. In a series of 322 GISTs [19], 80.9% showed *KIT* mutations, while 7.1% showed *PDGFRA* mutations, and 12% were wild-type. Recent data indicate that the clinical response of GIST to the tyrosine kinase inhibitors is determined by the specific mutation displayed by their tumours. Limited therapeutic effect has been described in PDGFRA exon 18 mutant tumours affecting the activation loop compared to those with PDGFRA exon 12 mutations at the juxtamembrane domain that usually demonstrates a similar response to GISTs with KIT exon 11 mutations. Recently, the promising role of FDG PET in assessing disease activity has been demonstrated in GISTs that are c-KIT negative but PDGFRA mutation positive [26]. An observation that we have made (unpublished data) is the visualization of bone marrow in a sizeable fraction of untreated GIST patients. Except for one patient (where polycythaemia rubra vera was associated) [27], there was no clear-cut pathological condition that could be related to this observation (bone marrow biopsies carried out in a few patients were negative for any pathological condition). Quite a few of them in this subpopulation had a history of gastrointestinal bleeding as the presenting complaint and had a haemoglobin level that was low or at the lower level of normal limits at the time of FDG PET study. It is not clear at this point whether this bone marrow FDG uptake in untreated GIST patients could be related to the rejuvenating marrow in response to blood loss or whether it is something specific to this group of tumours in this subpopulation of patients with GIST.

Newer therapeutic agents [28, 29] are on the horizons that are being particularly tested in the imatinib-resistant tumours. These include heat shock protein 90 (a chaperone, implicated as master regulator of KIT in the GIST cell) inhibitors [28] and the histone deacetylase (HDAC) inhibitors that result in KIT oncoprotein destruction irrespective of the imatinib resistance status and flavopiridol [29] that blocks KIT gene transcription and thus impairs KIT synthesis. It is perceivable that the clinical efficacy of these novel therapeutic agents can also be objectively monitored by PET imaging with FDG and possibly other novel tracers.

Thus, with the potential of addressing multiple concerns effectively, the promise of PET-based molecular imaging in managing patients with GISTs will be increasingly realized that will be well beyond its proven role in monitoring therapeutic response. It is imperative that this will lead to further enhancement of molecular imaging-based GIST

research and therapeutics that is presently at the forefront of the advances in the personalized medicine in the practice of oncology.

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