

F18-FDG-PET PROVIDES EARLY EVIDENCE OF BIOLOGICAL RESPONSE TO STI571 IN PATIENTS WITH MALIGNANT GASTROINTESTINAL STROMAL TUMORS (GIST)

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Abstract

The purpose of this study was to evaluate the role of F18-FDG-PET (FDG-PET) imaging in comparison with standard anatomical imaging using CT in monitoring response to STI571 in patients with advanced gastrointestinal stromal tumor (GIST). CT and attenuated-corrected 2-D whole body FDG-PET were performed in 25 patients at baseline. All patients had subsequent FDG-PET scans and CT scans (1 to 7 studies/patient) between 24 hours and 9 months after initiation of daily oral therapy. Interpreters were blinded to the results of the other imaging modality. F18-FDG uptake was assessed using standard uptake values (SUVs) and tumor-to-background ratios (TBRs). Bi-dimensional measurements were used for CT. Sites of disease defined by CT at baseline correlated with areas of abnormality on FDG-PET. FDG-PET showed additional sites of disease, metabolic activity within tumor sites, and response to therapy as early as 24 hours following initiation of therapy. Lack of metabolic response on FDG-PET was noted in 5/25 patients: one of these patients exhibited primary resistance to STI571 with tumor progression by CT and conventional clinical criteria, while the others demonstrated either stable or progressive disease by morphologic criteria. The mechanisms behind FDG-PET changes are under study, and the roles and correlative evaluation of FDG-PET and CT will need to be further studied prospectively to assess the respective predictive value of each test. These findings suggest that the functional information provided by FDG-PET may play an important role in the evaluation of therapies such as STI571, which target specific cell-signaling mechanisms. (Sponsored by Novartis Oncology)

range: 300-810 MBq, standard deviation = 73 MBq) was then administered intravenously and patients were asked to rest for a mean uptake period of 50 minutes (range: 28-125 minutes, standard deviation = 13 minutes). Following voiding, they were then positioned supine on the camera table with their arms extended outside of the field of view. Patients were scanned from the base of the skull to the proximal thighs using a multiple-bed whole-body protocol. Emission data were acquired for 7 minutes at each bed position, with the septa extended into the field of view. Transmission data were acquired for 3 minutes at each bed position using the rotating positron emitting rod sources supplied with the system. Data were reconstructed using a segmented attenuation correction (Xu et al, 1996), and an attenuation-weighted ordered-subsets expectation-maximization (OSEM-AW) reconstruction algorithm based on the work of Hudson and Larkin (1994). Eight subsets and two iterations were employed, and a post-reconstruction smoothing was applied. The smoothing kernel was a 3-D Gaussian of width dependent on patient weight (see Table 1). The reconstructed images were rebinned into image volumes with cubic voxels of side 0.51 cm. The reconstructed data were also used to create maximum-intensity projection images for cine viewing.

Patient weight	Kernel full-width at half-maximum
less than 68.2 kg	6 mm
between 68.2 kg and 90.9 kg	7 mm
between 90.9 kg and 113.6 kg	8 mm
between 113.6 kg and 136.4 kg	9 mm
136.4 kg and above	10 mm

Table 1: Patient weights and Gaussian smoothing filters applied

Standard uptake values (SUVs) and Tumor-to-background ratios (TBRs)

SUVs (Strauss and Conti 1991) and TBRs were calculated for the lesion with the most intense uptake at baseline, and subsequently calculated for the same lesion on follow-up scans.

Baseline SUVs were calculated using the following methodology: first, the image plane containing the maximum pixel intensity for the selected lesion was identified. Then a region of interest (ROI) was drawn on the lesion, with the boundary set to 70% of the lesion maximum. Finally, the SUV within the ROI was calculated using the following formula:

$$\text{SUV} = \text{mean pixel value (Bq/cc, decay corrected to start of scan)} \times (\text{patient weight [kg]}) \times 1000 / \text{injected dose (Bq)}$$

No corrections for partial volume effects or blood glucose level were applied.

Baseline TBRs were calculated as follows: for each selected lesion, the mean tumor pixel value was calculated from the ROI used to calculate the SUV. Four additional ROIs of size similar to the lesion ROI were then placed on normal tissue close to the lesion and/or within the organ containing the lesion. The mean normal tissue pixel value was then computed from these four ROIs. The TBR was then calculated by dividing the mean tumor pixel value by the mean normal tissue pixel value.

The methodology for defining baseline ROIs could not be used in the follow-up images because of the very substantial changes in lesion uptake encountered. Follow-up SUVs and TBRs were therefore calculated by duplicating the ROIs used in the baseline study and placing them over the operator's best estimate of the same location in the follow-up images.

Baseline studies

The results showed that prior to any STI571 therapy, most GIST demonstrated high glycolytic activity with a mean SUV of 5.2 (range 1.5 to 13.4). The average TBR at baseline was 4.5 (range 1.3 to 11.7) (Figure 1). The highest glycolytic activity was usually seen at the periphery of the tumor masses, while the centers of these masses were relatively photopenic.

Sites of disease defined by CT at baseline correlated with areas of abnormal glycolytic activity on FDG-PET, but FDG-PET provided additional information regarding the extent of disease. Most of the tumors were located in the abdomen, liver, and pelvis (Figure 2A). Several patients demonstrated additional bone marrow involvement, as well as soft tissue involvement outside of the abdominal and pelvic regions (Figure 2B).

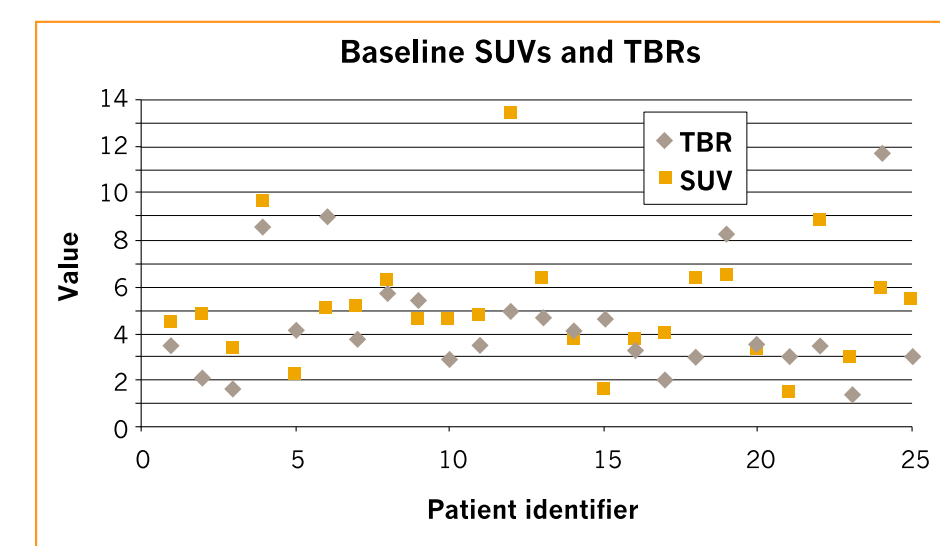


Figure 1: Ranges of SUV and TBRs at baseline (n = 25 patients)

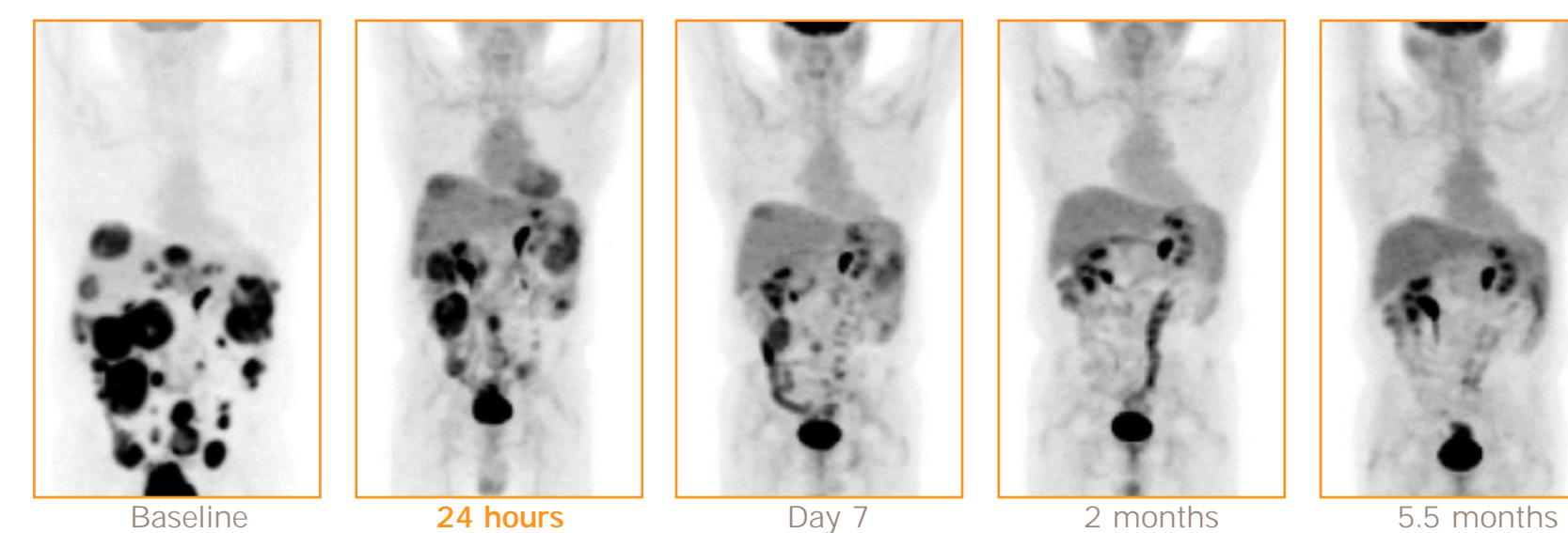


Figure 2A: FDG-PET studies in a patient showing extensive, highly FDG-avid abdominal and hepatic disease at baseline. Follow-up studies demonstrate evidence of response as early as 24 hours post-initiation of STI571 therapy, continuing response at 7 days, and no evidence of FDG-avid disease on the 2 and 5.5 months follow-up scans.

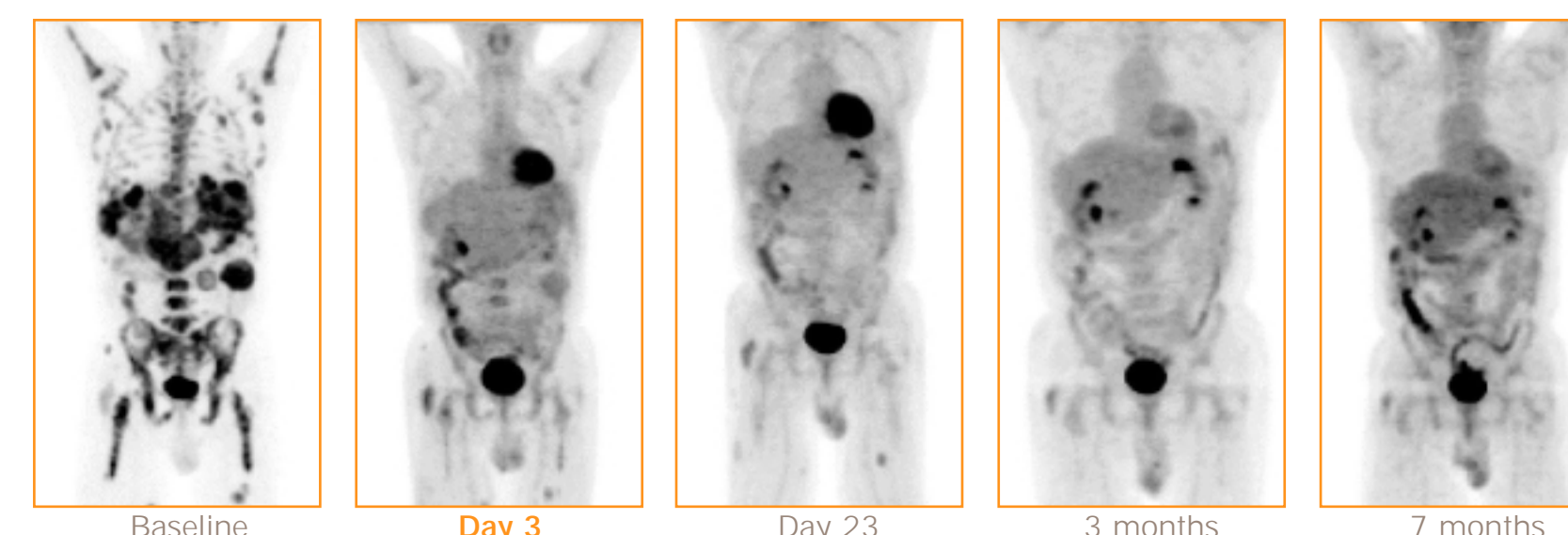


Figure 2B: FDG-PET studies in a patient with extensive, highly FDG-avid abdominal, hepatic, bone marrow, and soft tissue involvement at baseline. Follow-up studies show evidence of response as early as 3 days following the initiation of therapy, and continuing response over time with no evidence of FDG-avid disease on the 7-month follow-up scan.

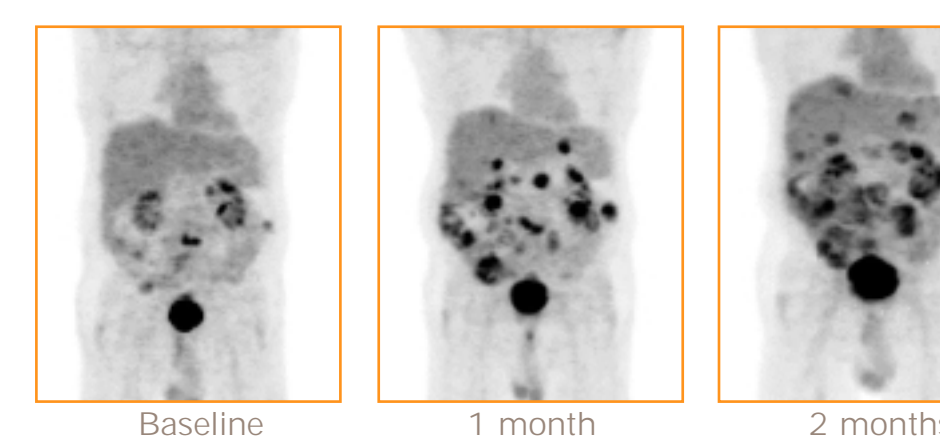


Figure 3: FDG-PET studies in the only patient who progressed following the initiation of STI571 therapy showing progressive FDG-avid disease in the liver, abdomen, and pelvis over time.

Results

Follow-up studies

Following the initiation of STI571 oral therapy, 80% of patients (20/25) demonstrated response based on qualitative evaluation of the PET images (Figure 2A/B). Only one patient exhibited primary resistance to STI571 with tumor progression as shown in Figure 3.

A significant decrease in SUV (52%) and TBR (57%) could be observed as early as 24 hours following the oral administration of a single dose of STI571. This early response was sustained and continued to improve up to 7 months following initiation of therapy. With the exception of one patient who demonstrated repeated hyperinsulinemic states, the qualitative evaluation of response to treatment was confirmed by TBR measurements (Figure 4). The maximum response seen was a decrease of approximately 95% in both SUV and TBR at 6 months.

All patients but one who showed complete response by PET criteria also showed decrease in tumor volume as estimated by CT one month following initiation of therapy. The overall decrease in tumor size based on bi-dimensional CT measurements ranged from 39% to 91% (Figure 5). The findings for the only patient who responded by PET, but did not show decrease in CT measurements may possibly be explained by intratumoral hemorrhage. Six patients remained stable or progressed on STI571 therapy based on CT criteria (Figure 5). The study findings are summarized in Table 2.

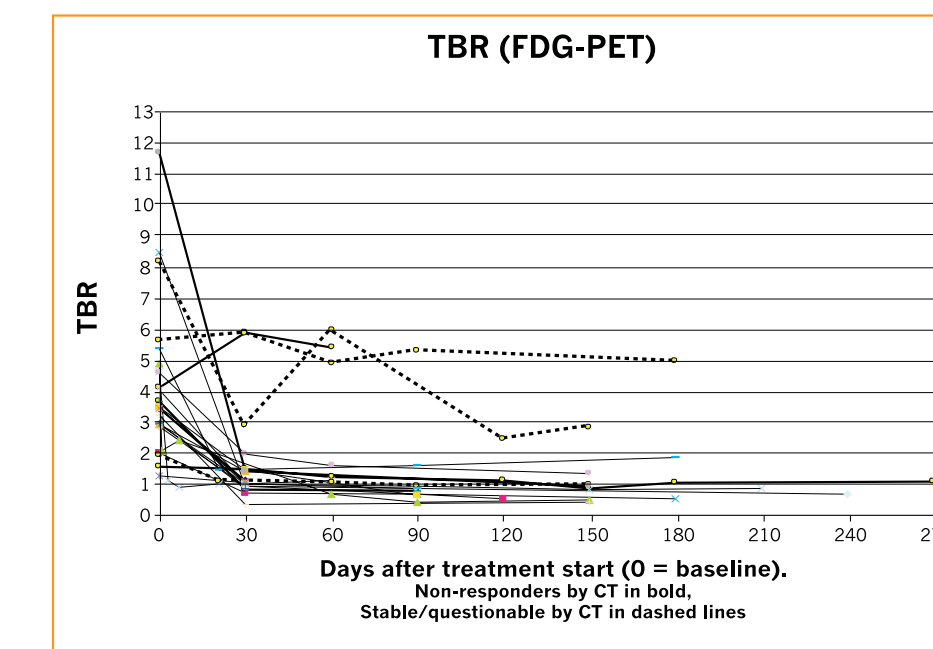


Figure 4: TBRs at baseline (0 = baseline) and following initiation of STI571 therapy for each patient.

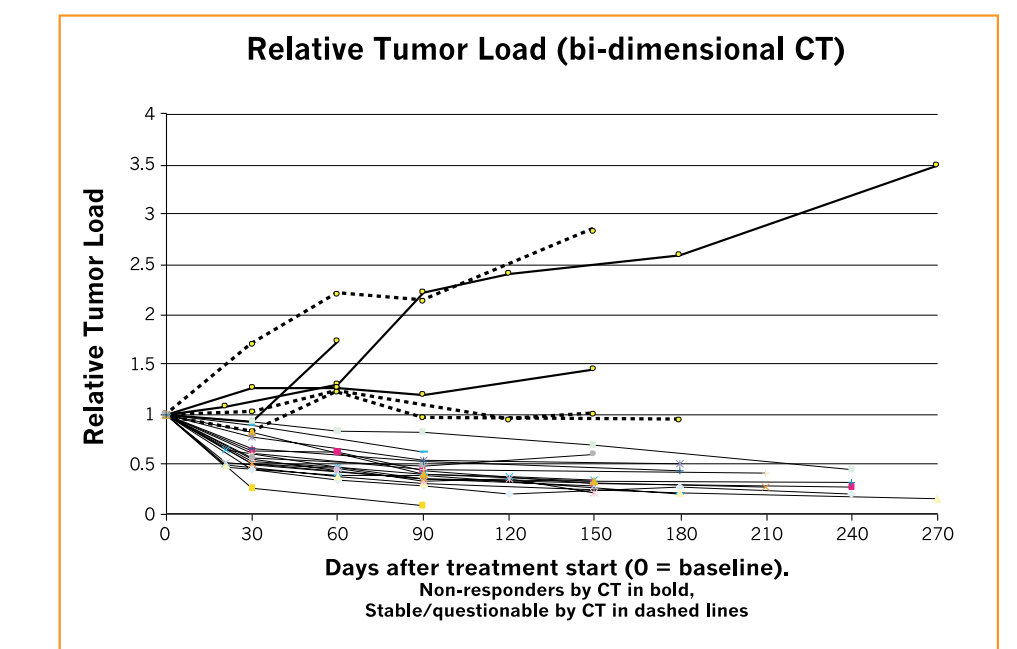


Figure 5: Morphologic measurements on CT at baseline and following initiation of STI571 therapy for each patient.

CT	TBR	PET	n =	Outcome
Decreased	Decreased	Complete response	19/25	Continuing therapy
Stable	Stable	Stable	1/25	Continuing therapy
Stable	Mild decrease	Partial response	1/25	Continuing therapy
Increased (possible intratumoral hemorrhage)	Decreased	Complete response	1/25	Continuing therapy
Increased	Decreased (but hyperinsulinemic, possible false negative)	Progression	1/25	Off study
Increased	Mild decrease	Partial response	1/25	Off study
Increased	Increased	Progression	1/25	Off study

Table 2: Summary of findings

Conclusions

- Most GIST tumors demonstrate high glycolytic activity at baseline prior to STI571 therapy.
- Sites of disease defined by FDG-PET at baseline correlated with areas of abnormality seen on CT. FDG-PET provided additional information regarding extent of disease.
- Response to STI571 therapy could be demonstrated by FDG-PET as early as 24 hours following initiation of therapy.
- In patients with stable or progressive disease, concordant findings between FDG-PET and bi-dimensional CT were seen in all but one case. The roles and correlative evaluation of FDG-PET and CT will need to be further studied prospectively to assess the respective predictive value of each test.
- These findings suggest that the functional information provided by FDG-PET may play an important role in the early evaluation of therapies that target specific cell-signaling mechanisms, such as STI571.

(Sponsored by Novartis Oncology)

References

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