In this phase I/II trial, 97 adult male and female patients 0–2 received SU11248 orally once daily for 14 or 28 days failed due to resistance or intolerance.10 While the efficacy benefit in GIST patients for whom imatinib therapy had demonstrated efficacy as first-line therapy for GIST.2 imatinib-resistant GIST treated with SU11248.11 The present study evaluated the ability of SU11248 to inhibited PDGFRs (PDGFR-α and β), glial cell-line derived neurotrophin factor (arranged during transfection; RET) and Fms-like tyrosine kinase-3 receptor (FLT3).13–15 In a recent phase III trial, SU11248 demonstrated clinical benefit in GIST patients for whom imatinib therapy had failed due to resistance or intolerance.11 While the efficacy of SU11248 in imatinib-resistant GIST patients may be due to different KIT binding, it is also possible that this activity in these patients is related to inhibitory effects on other RTKs, namely PDGFRs and VEGFRs.2

The present study evaluated the ability of SU11248 to inhibit PDGFR-β and VEGFR-2 activity in patients with imatinib-resistant GISTS and examined the relationship between this inhibitory activity and clinical benefit. The study also evaluated the ability of SU11248 to induce apoptosis of tumor cells and endothelial cells (particularly related to angiogenesis), and related this to clinical benefit.

Materials and Methods

In this phase III trial, 97 adult male and female patients with metastatic imatinib-resistant GIST and EOCG status 0–2 received SU11248 orally once daily for 14 or 28 days followed by 14 days without treatment per cycle. Biopsies were obtained at baseline and 3 days after initiating therapy in 20 of the patients.

Quantitative analysis of RTK expression and activity in tumors was performed using laser scanning cytometry (LSC) detection of fluoresecence labeled total and phosphorylated RTKs, as described previously.2 Active RTKs were measured using phosphorylation-site specific antibodies.3,4

Correlation of RTK Activity with Clinical Response

Phosphorylated PDGFR-β (reflecting PDGF receptor activity) decreased by 18% in patients in which SU11248 therapy was associated with clinical benefit (Figure 1). When taken together and analyzed quantitatively (Figure 3), inhibition of PDGFR-β and VEGFR-2 phosphorylation appeared to be associated with clinical benefit, while increased RTK phosphorylation appeared to be associated with disease progression.

Table 1 presents the correlation between change in RTK activity and clinical benefit. PDGFR-β and VEGFR-2 phosphorylation significantly decreased from baseline in patients experiencing clinical benefit on SU11248 therapy. Table 1 presents the correlation between change in RTK activity and clinical benefit. PDGFR-β and VEGFR-2 phosphorylation significantly decreased from baseline in patients experiencing clinical benefit on SU11248 therapy. The relationship between PDGFR-β phosphorylation increased significantly in patients experiencing disease progression on SU11248 therapy, while there was a trend toward increased PDGFR-β phosphorylation compared with baseline in these patients.

Correlation of Tumor Apoptosis with Clinical Response

Apoptosis generally considered to be the driving force in the pathogenesis of GISTs.1 Apoptosis was increased by 10- and 6-fold (P<0.05) increase from baseline in patients in whom SU11248 therapy was associated with clinical benefit (Figure 2).

Conclusions

Inhibition of PDGFR-β and VEGFR-2 activities (as assessed by decreased RTK phosphorylation) or induction of tumor and endothelial cell apoptosis appear to be biomarkers of clinical benefit in patients with imatinib-resistant GIST treated with SU11248.12 These data suggest that activity of SU11248 against PDGFR-β and VEGFR-2 may play an important role in the antitumor effects of SU11248 in patients with imatinib-resistant GIST. We hypothesized that the multi-targeted nature of SU11248 results in the inhibition of RTKs on both tumor and vascular endothelial cells. Additional work is required to better describe potential biomarkers of SU11248 activity in this patient population. Other potential biomarkers include blood-borne endothelial cells, monocytes, soluble VEGF-2, and VEGF.

References