Blood-Based Biomarkers of SU11248 Activity and Clinical Outcome in Patients with Metastatic Imatinib-Resistant Gastrointestinal Stromal Tumor

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Abstract

Purpose: There is an unmet need for noninvasive markers to measure the biological effects of targeted agents, particularly those inhibiting the vascular endothelial growth factor (VEGF) receptor (VEGFR) pathway, and identify patients most likely to benefit from treatment. In this study, we investigated potential blood-based biomarkers for SU11248 (sunitinib malate), a multitargeted tyrosine kinase inhibitor, in patients with metastatic imatinib-refractory gastrointestinal stromal tumors.

Experimental Design: Patients (n = 73) enrolled in a phase I/II trial received SU11248 daily for 14 or 28 days followed by 14 days without treatment per cycle. Clinical benefit was defined as progression-free survival of 6 months. We assessed plasma markers, including VEGF and soluble VEGFR-2 (sVEGFR-2), and two cellular populations bearing VEGF receptors: monocytes and, in a subset of patients, mature circulating endothelial cells (CEC).

Results: Compared to patients with progressive disease, patients with clinical benefit had significantly greater increases in CECs (0.52 versus −0.01 CEC/μL/d, P = 0.03) and smaller decreases in monocyte levels (47% versus 60%, P = 0.007) during cycle 1. VEGF increased by 2.2-fold and sVEGFR-2 decreased 25% during the first 2 weeks of treatment. Neither plasma marker correlated with clinical outcome although a modest inverse correlation was observed between sVEGFR-2 changes and plasma drug levels. Monocytes, VEGF, and sVEGFR-2 all rebounded towards baseline off treatment.

Conclusions: Monocytes, VEGF, and sVEGFR-2 were consistently modulated by treatment, suggesting that they may serve as pharmacodynamic markers for SU11248. Changes in CECs and monocytes, but not the plasma markers, differed between the patients with clinical benefit and those with progressive disease. These end points merit further investigation in future trials to determine their utility as markers of SU11248 activity and clinical benefit in gastrointestinal stromal tumors and other tumor types.

Targeted agents such as inhibitors of the vascular endothelial growth factor (VEGF) pathway have shown evidence of clinical activity in a variety of malignancies including colorectal, lung, and renal cell cancer (1–3). Despite this activity, it has been difficult to assess the biological effects of these agents as they seem to be primarily cytostatic when used as monotherapy. To optimize the clinical testing of these agents, there is an unmet need for validated biomarkers to measure their biological effects, determine their optimal dose level, identify patients most likely to benefit from a given agent, and monitor responses to treatment (4, 5).

One approach for assessing the biological activity of targeted agents is to evaluate drug-induced effects on tumor cells or the vasculature (6, 7). However, because this approach is invasive, it is not practical for routine clinical use. The development of blood-based or other noninvasive biomarkers would represent a significant advance.

Circulating endothelial cells (CEC) have emerged as a potentially useful biomarker for several reasons (8–13). Increased levels of CECs have been observed in cancer patients (14, 15), they are known to be mobilized in response to VEGF (16–18) and express VEGFR-2 (19, 20). At least two distinct populations of CECs have been identified: bone marrow–derived circulating endothelial progenitors (CEP), which may contribute to tumor neovascularization (21), and mature CECs, which are thought to be shed from established vessels (22, 23). Recently, we have shown that in
murine models, VEGF pathway inhibitors can have differential effects on mature CECs and CEPs, and that inhibition of tumor angiogenesis is accompanied by an increase in mature CECs (11). Consistent with this model, a recent study suggests that an increase in apoptotic CECs, thought to be shed from the tumor vasculature, is associated with improved outcome in breast cancer patients receiving metronomic chemotherapy (13).

Levels of VEGF and soluble VEGFR-1 have been investigated in serum, plasma, or urine in clinical trials with mixed results (6, 24, 25). Recently, a soluble form of VEGFR-2 (sVEGFR-2) has been identified and was found to be elevated in cancer patients (26–29).

In this study of patients with imatinib-resistant metastatic gastrointestinal stromal tumor (GIST), we sought to identify potential biomarkers for sunitinib malate (SU11248, Sutent; Pfizer, Inc., New York, NY), a multitargeted receptor tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor, KIT, and FLT-3 (30). Substantial clinical activity was observed in this study, with 54% of patients experiencing clinical benefit defined as objective response or progression-free survival for >6 months and partial tumor responses in 13% (31, 32). We examined baseline levels (prior to SU11248 treatment) and posttreatment changes in plasma VEGF and sVEGFR-2 levels, as well as two cellular markers, CECs and monocytes, which are known to express VEGFRs (33, 34). We show that all of these markers change after SU11248 administration and that for two of them—CECs, and monocytes—these changes correlated with clinical outcome.

Patients and Methods

Patients and study design. Patients enrolled in an Institutional Review Board–approved protocol for a phase I/II study of SU11248 for metastatic or unresectable GIST. All patients had objective evidence of disease progression prior to enrollment and were resistant, refractory, or intolerant to imatinib mesylate. Patients were ≥18 years old and signed an informed consent. Two main schedules of drug administration were used: 4 weeks of treatment followed by a 2-week rest period (4/2 schedule) or 2 weeks of treatment followed by a 2-week rest period (2/2 schedule). Patients received doses of 25, 50, or 75 mg of SU11248 per day orally. All patients for whom biomarker data is presented in this study were treated with the 50 mg dose with the exception of the monocyte analysis. For this analysis (n = 73 total), 64 patients received 50 mg, 5 patients received 25, and 4 patients received the 75 mg dose. Clinical benefit (CB) was defined as progression-free survival ≥6 months, and progressive disease (PD) defined as progression-free survival <6 months. Samples were analyzed blinded to clinical outcome. Blood was also obtained from healthy volunteers who consented to an Institutional Review Board–approved protocol.

Plasma markers and pharmacokinetic assessments. Plasma VEGF and sVEGFR-2 levels were quantified by ELISA kits (R&D Systems, Minneapolis, MN; ref. 26). The assays were run under Good Laboratory Practice conditions at Alta Analytical Laboratory (San Diego, CA) and the performance specifications of each ELISA were validated (35). Pharmacokinetic analyses of SU11248 and its major active metabolite, SU12662, were done by means of a validated and sensitive liquid chromatography–mass spectrometry–mass spectrometry method as previously described (36). The lower limits of detection for the assay were 0.099 ng/mL for SU11248 and 0.088 ng/mL for SU12662.

Antibodies for flow cytometry. Anti–human VEGFR-1-APC and VEGFR-2PE were purchased from R&D Systems. CD14-PE, CD31-FITC, and CD45-PerCp were purchased from BD Biosciences (San Jose CA). CD133-APC and CD14-FITC were purchased from Miltenyi Biotec (Auburn, CA). P1H12-PE (CD146-PE) was purchased from Chemicon (Temecula, CA).

VEGF binding and receptor expression in peripheral blood mononuclear cells. Blood was collected in EDTA tubes and peripheral blood mononuclear cells (PBMC) were isolated by density gradient (Histopaque 1077; Sigma, St. Louis, MO). Cells were incubated with biotinylated rhVEGF followed by Avidin–FITC as a secondary antibody (Fluorokine Kit, R&D Systems) and additional antibodies as indicated. For VEGFR-1 and VEGFR-2 staining, red cell lysis was done using FACSlyse solution (BD Biosciences). Flow cytometry was done using a FACSCalibur (BD Biosciences) and data analyzed using FlowJo (Tree Star, CA).

Measurement of CECs. Blood was collected and PBMCs were isolated by Ficoll gradient as described above. Freezing medium (40% RPMI 1640, 10% DMSO, 50% plasma) was added to the cell pellet and samples underwent a controlled freeze using an isopropanol bath in a -80°C freezer. Samples were then stored in liquid nitrogen until the day of analysis. This method yielded >85% viable cells after thawing (data not shown). For each patient, all samples (baseline and subsequent follow-ups) were thawed and analyzed at the same day to minimize interassay variability. CECs were enumerated using four-color flow cytometry as described previously (15) with the modifications described below. Briefly, cells were washed with PBS with 1% albumin and incubated with a panel of four antibodies to establish markers including CD45, CD31, CD146, and CD133 (13, 15, 19, 37). CECs were defined as negative for hematopoietic marker CD45, positive for endothelial markers CD31 and CD146, and negative for the progenitor marker CD133; CEPs had the same phenotype but were CD133+. Human umbilical vein endothelial cells (Cambrex, East Rutherford, NJ) were used as positive control for CD146 staining and WERI cells (American Type Culture Collection, Manassas, VA) as positive controls for CD133. The percentage of stained cells was determined comparing with appropriate isotype controls. The volume of blood analyzed was determined using the lymphocyte and monocyte numbers obtained from the patient's differential blood count.

Statistical analysis. Descriptive statistics were used to characterize cell counts and percentage changes. For all comparisons, except those involving CECs, values were approximately normal in distribution and are presented as means with SEs. For these comparisons, Student’s t tests were used for testing the significance. For counts that were not normally distributed (CECs), medians and interquartile ranges are provided. The Wilcoxon signed rank test was used to explore changes over time. The Mann-Whitney test (Wilcoxon rank sum test) was used to test for differences in the percent change between patients experiencing CB and those who did not, and between treated patients and normal controls. P ≤ 0.05 was considered statistically significant. All tests were two-sided.

Results

Plasma levels of VEGF and sVEGFR-2 change in patients with GIST during treatment with SU11248. We first investigated plasma VEGF and sVEGFR-2 as biomarkers for SU11248. At baseline, the mean plasma levels of VEGF and sVEGFR-2 were 104 pg/mL (range, 23-355) and 8,350 pg/mL (range, 5,822-14,245), respectively. There was no significant difference between the CB and PD groups at baseline for either marker, although a trend was observed for VEGF (86.8 pg/mL for CB versus 120.2 pg/mL for PD groups, P = 0.3).

We then investigated changes in plasma markers during treatment with SU11248. The drug was administered once daily on two schedules, 2 weeks on treatment followed by 2 weeks of rest (2/2 schedule) or 4 weeks on treatment followed by 2 weeks of rest (4/2 schedule). This permitted us to assess changes in biomarkers both during the first 2 weeks of...
treatment in the two groups combined, during which time patients in both groups received identical treatment. After the first 2 weeks of cycle 1, VEGF levels increased significantly by 2.2-fold from baseline \((P = 0.008)\). sVEGFR-2, in contrast with VEGF, decreased significantly to 75% of baseline over the first 2 weeks of treatment \((P < 0.001)\). The increase in VEGF, and the decrease in sVEGFR-2, did not differ between the CB and PD groups, but after 2 weeks of treatment, the decrease in sVEGFR-2 showed a modest inverse linear correlation with trough plasma drug levels of SU11248 and its major metabolite SU12662 \((R^2 = 0.33;\) Fig. 1C).

Overall, VEGF and sVEGFR-2 continued to change in a reciprocal manner and the changes during treatment reversed directions during the rest period for both groups. This pattern is illustrated for the 4/2 group in Fig. 1A and B. These changes were consistently observed through four cycles of treatment. A similar pattern was observed for the 2/2 group (data not shown).

### Screening of PBMCs expressing VEGFRs.

We next investigated potential blood-based cellular markers for SU11248 activity. Given the pan-VEGFR inhibition by SU11248, we started by screening peripheral blood from normal volunteers to identify VEGF-binding cells that might be useful as biomarkers. As seen in Fig. 2A, VEGF binding was predominantly observed in mononuclear cells positive for the monocyte marker CD14; out of the total CD14+ population, 65.3% showed VEGF binding, as compared with only 5.3% of CD14- cells. These VEGF-binding cells were also identified as monocytes based on their forward and side scatter characteristics (data not shown). The majority of CD14+ cells expressed VEGFR-1 (Fig. 2B) and <1% of these cells were VEGFR-2+ (Fig. 2C). Only 5% of CD14- cells expressed VEGFR-1 (Fig. 2D). Therefore, the majority of VEGF binding to PBMCs was observed on CD14+ monocytes, which express VEGFR-1 but not VEGFR-2. Limited VEGFR-1 staining was also observed on neutrophils (data not shown). These results suggest that CD14+ monocytes are the major VEGF-binding population in peripheral blood, consistent with their known expression of VEGFR-1. We also assessed VEGFR-1 and VEGFR-2 expression in CD45-/P1H12+ CECs. VEGFR-1 and VEGFR-2 staining was detected in 47% and 50% of CECs, respectively, with 19% staining for both antigens (Fig. 2E).
changes in CECs and monocytes in patients treated with SU11248.

Monocyte counts decrease in patients with GIST during treatment with SU11248. We investigated the changes in the number of monocytes and other peripheral blood cell types in 73 patients treated for 2 weeks with SU11248 (both 2/2 and 4/2 schedule; Fig. 3A) during cycle 1. Total WBC count dropped from a mean of 8,320 to 6,430 cells/μL (20.4%, \( P < 0.001 \); Student’s \( t \) test). Monocytes underwent the largest proportionate decrease, from a mean of 770 to 350 cells/μL (53.7%, \( P < 0.001 \)). Neutrophils were among other cell types that decreased during this period, albeit to a lesser extent (20.3%). After a period of 2 weeks rest, only monocytes increased significantly, from a mean of 340 to 520 cells/μL (95.6%, \( P < 0.001 \)). This pattern continued during subsequent cycles, as shown for the 32 patients treated in the 4/2 group in Fig. 3B. A similar pattern was observed in the 2/2 group (data not shown). Lymphocytes, in contrast, did not change significantly over time. Baseline monocyte levels did not differ between the CB and PD groups, but after the first 2 weeks of treatment in cycle 1 patients with CB had a significantly smaller decrease in monocytes compared with the PD group (60.4% versus 47.4%, \( P = 0.007 \); Fig. 3C).

There were no significant differences in the changes observed in patients receiving 25 mg (\( n = 5 \)), 50 mg (\( n = 64 \)) or 75 mg (\( n = 4 \)), although there was a limited power to detect differences given the small sample number of patients in the 25 and 75 mg groups.

CECs in patients with GIST treated with SU11248. CECs were assessed by four-color flow cytometry using a panel of established antibodies as previously described (15), with modifications detailed in Patients and Methods (Fig. 4). CEC analyses were included in only a subset of the patients in the study (\( n = 16 \)) treated exclusively with the 50 mg dose using the 4/2 schedule because the sample preparation and analysis was done only at one study site (Dana-Farber Cancer Institute) and was introduced after enrollment in this cohort had started.

In normal controls (\( n = 15 \)), the median level of mature CECs was 0.54 CEC/μL (interquartile range, 0.37-0.69). For patients with GIST, median baseline levels of CECs were ∼2-fold higher [1.09 (0.67-3.54) CEC/μL; \( P = 0.01 \); Fig. 5].
the 16 GIST patients, 7 showed CB, whereas 9 had PD. At baseline, there was no significant difference in CEC levels between these two groups (0.93 versus 1.21 CECs/μL; \( P = 0.37 \), respectively).

Next, we assessed changes in CECs during SU11248 treatment (Fig. 6A). Overall, the median CEC number increased by 3.5-fold during the first cycle of therapy. All seven patients with CB had an increase in their CEC numbers between baseline and a second sample taken 6 to 20 days after the initiation of SU11248 to a median value of 3.97 (3.8-52.4) CEC/μL. In contrast, only three out of nine patients with PD displayed an increase in their CEC numbers, with the group median value decreasing to 0.45 (0.02-12.57) CEC/μL at first follow-up. Thus, there was a statistically significant difference in the rate of change in CECs per day between patients with CB and PD [0.52 versus -0.01 CEC/μL/d (0.3 to 8.1 versus -0.1 to 0.3, respectively); \( P = 0.03 \)]. In the majority of patients assessed, CECs returned to near baseline levels by the end of the first treatment cycle, as illustrated for two patients in Fig. 6B.

**Discussion**

A major obstacle in the clinical development of targeted agents, particularly those inhibiting the VEGF pathway, is the lack of noninvasive biomarkers for identifying patients most likely to respond to a given therapy or monitor response during treatment. As a step towards addressing these needs, we investigated plasma and peripheral blood cellular biomarkers for SU11248, a multitargeted tyrosine kinase inhibitor with activity against VEGFR-1, VEGFR-2, and VEGFR-3, and other receptors. This work focused on biomarkers from the VEGF pathway.

We observed that plasma VEGF levels increased by ~2.2-fold on average after the first 2 weeks of treatment, then decreased to near baseline levels after the 2-week rest period and repeated a similar pattern during subsequent cycles. In previous reports, the levels of plasma, serum, or urine VEGF have been evaluated before and during treatment with mixed results (6, 24, 38, 39). Interestingly, in preclinical models, an increase in VEGF was observed after treatment of either tumor-bearing or normal mice with a VEGFR-2 blocking monoclonal antibody, but not with small molecule VEGFR-2 inhibitors (5), implying that VEGF blockade at the level of the ligand versus the receptor can elicit different responses. Possible mechanisms for the changes observed in this study include the induction of hypoxia (in normal and/or tumor tissues), increased release of VEGF from existing stores (i.e., platelets), or alterations in VEGF clearance from blood. These results highlight the complexities in VEGF regulation and suggest that plasma VEGF may serve as a pharmacodynamic marker of antiangiogenic therapy but does not seem to be a predictive marker of CB in patients with GIST.

sVEGFR-2 was previously found to be elevated in patients with certain types of cancer (26, 28, 29). We investigated whether sVEGFR-2 may serve as a marker of activity of SU11248. In general, sVEGFR-2 changed in the opposite
direction to VEGF, decreasing on average to 75% of baseline value during the first 2 weeks of treatment, and rising to near-baseline after the rest period. The source of sVEGFR-2 remains unclear, but the striking inverse correlation with VEGF levels suggests a coregulation or link between the two changes. In sVEGFR-2 were inversely associated with trough plasma drug concentrations, although not strictly correlated. The pattern and magnitude of changes of sVEGFR-2 were similar between patients with CB and PD, suggesting that sVEGFR-2 may be useful as a pharmacodynamic marker of drug exposure but not CB in patients with GIST. Preliminary results from a phase I study of the pan-VEGFR inhibitor AZD2171 (40), and recently published results using SU11248 in a phase I study (41) and phase II study in patients with RCC (42), suggest that sVEGFR-2 may be a useful pharmacodynamic marker for other drugs targeting VEGFRs, and furthermore, have utility as a biomarker across other types of malignancies as well.

Next, we investigated cellular markers in the peripheral blood. As a starting point, we screened PBMCs for VEGF binding and identified monocytes as the major population (Fig. 2). As previously reported, monocytes were found to have VEGFR-1 but not VEGFR-2 immunoreactivity (43). The presence of VEGFR-1 and VEGFR-2 staining was also observed on CECs, although only a minority were doubly positive for both receptors (Fig. 2E). Because these two populations express VEGFRs, we hypothesized that they may serve as biomarkers of SU11248 activity.

To test this hypothesis, monocytes were evaluated in all patients, whereas CECs were evaluated in a subset of patients enrolled in a phase I/II trial of SU11248 for metastatic, imatinib-resistant GIST. Patients were treated with an intermittent dosing schedule, which provided an opportunity to observe changes during both treatment and rest periods. Monocytes underwent the largest proportional decrease of any PBMC population after the first 2 weeks of treatment (Fig. 3A). Furthermore, monocytes subsequently underwent the largest proportional increase during the 2-week rest period, and this pattern continued throughout the treatment duration. By contrast, lymphocytes and other PBMC populations did not change to a similar extent during this time period, suggesting that the decrease in monocytes was unlikely to be due solely to a generalized bone marrow effect. There was, however, a 14% rate of grade 3 or 4 neutropenia observed overall, suggesting that the drug did have at least some effect on other PBMC populations over time (31).

There are several potential explanations for the SU11248-induced decrease in monocytes and, to a lesser extent, neutrophils. VEGFR-1 is known to be involved in monocyte migration (34) and has been implicated in hematopoietic reconstitution after chemotherapy, particularly in the recovery of the myeloid lineage which include both monocytes and neutrophils (44). Other targets of SU11248 that might play a role include c-KIT, FLT-3, platelet-derived growth factor receptor-α and -β, which are all known to be expressed on monocytes or granulocytic/monocytic precursors (34, 43, 45–49). Consistent with this possibility, impaired growth of monocyte/macrophage colonies was observed after treatment with imatinib, an inhibitor of c-KIT and PDGR (45). Other studies have shown that Flt-3 has a stimulatory effect on hematopoietic stem cells and a specific proliferative/differentiative action on granulocytic/monocytic precursors when combined with KIT-ligand and macrophage-specific colony-stimulating factor (46).

In this study, the patients with PD had a larger decrease in their monocyte counts after the initial 2 weeks of treatment with SU11248 compared with patients with CB. This observation is, at first glance, counterintuitive. It might be expected that a reduction in monocyte levels would be associated with a higher degree of target inhibition and greater clinical efficacy. The mechanism underlying this phenomenon is unknown. One possible explanation is that for patients with CB, there may be greater SU11248 binding and uptake by the tumor because of the presence of increased levels of target receptors (i.e., VEGFR and KIT), leaving less unbound drug circulating in the plasma. The observation merits further investigation.

We also investigated changes in CECs in a subset of 16 patients at baseline and during treatment with SU11248. Consistent with earlier reports from patients with other malignancies, we found that at baseline, CECs were elevated in patients with GIST compared with normal controls (15). The median levels observed for normal controls (0.55 CEC/μL) was similar to previously reported levels measured by flow cytometry (50). There was no significant difference in CECs at baseline between the two outcome groups, although given the sample size, there was a limited power to detect modest differences. CEPs were present at significantly lower levels than mature CECs in all patients and were undetectable in some patients. No consistent pattern of change in CEPs was observed (data not shown). Future studies may require a higher number of events (i.e., >500,000 PBMCs per analysis) to obtain reliable CEP data.

Interestingly, an increase in CECs was observed in seven of seven patients with PD during the first cycle as compared with four of nine patients with PD (Fig. 6A). The changes in CECs could be observed after a week of treatment but it seemed that such changes may be transient in at least some cases. This finding, and other recent studies, suggest that more detailed kinetic studies should be conducted to determine the optimal time for CEC measurement (12, 51). This is particularly relevant given the recent observations that changes in CECs may be observed within hours of treatment (52), whereas in other studies, changes have been observed a month or more after starting treatment (13).

Given that CECs were only assessed in a subset of patients retrospectively, it should be regarded as an exploratory rather than definitive analysis. Nevertheless, it does suggest that CECs merit further investigation in larger, preferably randomized studies. The findings are consistent with our previous study in which antiangiogenic treatment caused an increase in mature CECs, but not bone marrow-derived CEPs, in murine models (11). As an increase in mature CECs was seen in tumor-bearing mice, but non–tumor-bearing mice receiving the same treatment, we proposed a model in which these mature CECs were derived at least in part from the shedding of damaged tumor endothelium. In this study, CB was associated with an increase in mature CECs. Interestingly, CB was also associated with increased tumor endothelial apoptosis in a separate analysis of 20 paired tumor biopsies from the same clinical trial. Patients with CB experienced an 8-fold induction in tumor endothelial apoptosis after 11 to 14 days of treatment, which was significantly greater than the 1.8-fold induction observed in patients with PD (53). Taken together, these observations
suggest that CB is associated with an induction of tumor endothelial apoptosis and increase in mature CECs over the first 2 weeks of treatment, supporting the possibility that an increase in apoptotic CECs was associated with benefit in patients with breast cancer treated with metronomic chemotherapy (13). Furthermore, in a recent phase I study of the vascular targeting agent ZD6126, an increase in CECs was seen within the first day of treatment, which was thought to reflect damage to tumor endothelium. There are, however, other potential explanations for the observed changes. For example, increased VEGF levels during treatment may have prolonged the survival of CECs in the circulation (23, 54). It is worth noting, however, that VEGF levels rose similarly in the CB and PD groups, suggesting that VEGF levels did not solely account for the CEC changes observed in this trial. Additional studies are needed to further characterize the sources of these mature CECs.

In summary, we identified an approach that involves screening PBMCs for relevant molecular targets that may lead to the identification of novel markers for SU11248 and other targeted agents. Furthermore, we found that two plasma markers, VEGF and sVEGFR-2, as well as two cellular markers, CECs and monocytes, were modulated during treatment with SU11248 in patients with imatinib-resistant GIST. Changes in the cellular markers correlated with clinical outcome and sVEGFR-2 changes correlated inversely with plasma drug concentrations. These markers merit further investigation in larger studies to determine whether they will be useful for identifying patients likely to benefit from treatment with, and monitoring response to, SU11248 and other targeted agents in patients with GIST or other tumor types.

References

or resistant acute myeloid leukemia (AML) or not amenable to conventional therapy for the disease.


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