Sunitinib Therapy for Melanoma Patients with KIT Mutations

David R. Minor1, Mohammed Kashani-Sabet1, Maria Garrido2, Steven J. O’Day3, Omid Hamid3, and Boris C. Bastian2

Abstract

**Purpose:** Recent studies have shown activating KIT mutations in melanoma originating from mucosa, acral, or cumulative sun-damaged skin sites. We aimed to assess the predictive role of KIT mutation, amplification, or overexpression for response to treatment with the kinase inhibitor sunitinib.

**Experimental Design:** Tumor tissues from 90 patients with stage III or IV acral, mucosal, or cumulative sun-damaged skin melanoma underwent sequencing of KIT, BRAF, NRAS, and GNAQ genes, FISH analysis for KIT amplification, and immunohistochemistry of KIT protein (CD117). Patients with mutations, amplifications, or overexpression of KIT were treated with sunitinib and responses measured by Response Evaluation Criteria in Solid Tumors (RECIST).

**Results:** Eleven percent of the melanomas tested had mutations in KIT, 23% in BRAF, 14% in NRAS, and none in GNAQ. Of 12 patients treated with sunitinib, 10 were evaluable. Of the 4 evaluable patients with KIT mutations, 1 had a complete remission for 15 months and 2 had partial responses (1- and 7-month duration). In contrast, only 1 of the 6 patients with only KIT amplification or overexpression alone had a partial response. In 1 responder with rectal melanoma who later progressed, the recurring tumor had a previously undetected mutation in NRAS, which was found in addition to the persisting mutation in KIT. Interestingly, among patients with manifest stage IV disease, KIT mutations were associated with a significantly shortened survival time ($P < 0.0001$).

**Conclusions:** Sunitinib may have activity in patients with melanoma and KIT mutations; more study is needed. KIT mutations may represent an adverse prognostic factor in metastatic melanoma. Clin Cancer Res; 18(5): 1457–63. ©2012 AACR.

Introduction

Metastatic melanoma is resistant to chemotherapy, and an important avenue of therapeutic melanoma research has centered on the search for genetic changes in the cancer that promote tumor growth. These genetic changes may provide targets for successful pharmaceutical intervention. Curtin and colleagues (1) first described activating mutations in the receptor tyrosine kinase KIT in melanomas originating from certain primary sites: acral, mucosal, or cumulative sun-damaged skin (CSDS; refs. 2, 3). In gastrointestinal stromal tumors (GIST), KIT mutations are observed in about 85% of tumors, and these activating mutations lead to an activated KIT receptor that drives tumor growth. Small-molecule inhibitors of the KIT receptor have been found to be clinically active (4), leading to U.S. Food and Drug Administration approval of both imatinib and sunitinib for the treatment of GISTS. There is considerable overlap in the mutation spectra of KIT mutations found in GISTS and in melanoma, raising the possibility that KIT inhibition may also be a promising strategy for certain melanomas (5, 6). Several case reports of marked responses to imatinib in KIT-mutant patients with melanoma supported this notion (7–9) and a study from China showed responses in 6 of 30 patients (10). The recent multicenter trial described in the study by Carvajal and colleagues screened 295 patients for KIT mutations and had 6 responders in 25 evaluable patients with mutations treated with imatinib (11). Sunitinib is a potent inhibitor of mutant KIT with additional inhibitory effects on VEGF receptors (12) that potentially might make it more effective than imatinib against KIT-mutated melanoma. We aimed to study the mutational status of patients with melanoma with acral, mucosal, or CSDS primaries; correlate mutational status with KIT amplification and protein expression; and explore...
the clinical activity of sunitinib therapy in patients whose melanomas had mutations, amplifications, or overexpression of KIT.

Patients and Methods

Patients were eligible for molecular testing if they had stage III or IV metastatic melanoma that had arisen from primaries originating from the mucosa or acral or CSDS. CSDS was inferred from a primary site on the scalp, face, or neck and patient age and not necessarily verified by finding solar elastosis on biopsy specimens, as the primary tumor was not always available for review. Acral sites were defined as the non–hair-bearing skin of the palms and soles or the nail apparatus. Patients were eligible for treatment with sunitinib if molecular analysis showed a KIT mutation in exons 9, 11, 13, 17, or 18, any amplification of the KIT gene, or immunohistochemistry for CD117 showing strong or very strong staining in more than 50% of neoplastic cells. Patients were treated with sunitinib (50 mg/d), 4 weeks on and 2 weeks off, with dose modifications sequentially to 37.5 and 25 mg/d for grade III or IV toxicities. Our study enrolled patients between September 2007 and July 2010 and was approved by the Institutional Review Boards for the protection of human subjects at California Pacific Medical Center, University of California at San Francisco (San Francisco, CA), and the Angeles Clinic and Research Institute.

Clinical characteristics of the 12 patients treated with sunitinib are listed in Table 1.

Tumor responses were measured by computed tomographic scanning every 6 weeks using Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. Duration of response (DR) was defined as the time from the first documentation of objective tumor response (complete or partial responses) that was subsequently confirmed to the first documentation of objective tumor progression or death due to any cause. Patients were considered nonevaluable for response if they received less than 2 weeks of therapy with sunitinib. Fisher’s 2-sided exact test was used to compare differences between groups, and MedCalc 11.3 software was used to calculate Kaplan–Meier survival curves and log-rank tests.

Although not part of the original study design, we conducted an exploratory survival analysis of patients who had molecular testing using the Kaplan–Meier method. This analysis was restricted to patients with radiologic or clinical evidence of unresectable metastatic disease on the date of consent for the study (n = 79), included 11 of 12 patients treated with sunitinib, and measured survival from date of consent for molecular testing. The date of onset of metastatic disease was not collected.

FISH was carried out with the Vysis LSI 4q12 Tricolor probe and a reference probe for the X-centromere (Abbott Molecular). KIT was considered amplified if the copy number of the Tricolor probes exceeded the gender-corrected copy number of the reference in the majority of neoplastic cells. Allelic ratios were determined by dividing the peak height of the mutant allele by that of the corresponding wild-type allele of an electropherogram trace. Immunohistochemistry for CD117 was carried out using a mouse monoclonal antibody (Dako A4502) at 1:200 dilution, visualized with the Envision system (Dako) with AEC as a chromagen.

Our original biostatistical design called for 12 evaluable patients. However, we feel our sample size of 90 screened patients with 10 patients evaluable for response was adequate as we saw several objective responses, and patient accrual was difficult due to the small patient population and rapid deterioration of patients with KIT mutations making some patients with mutations ineligible for treatment.

Results

Laboratory results

We screened the tissues of 90 potentially eligible patients with metastatic melanoma for mutations or amplifications...
of KIT, as well mutations in BRAF, NRAS, and GNAQ. Forty-two (47%) of the 90 patients with melanoma analyzed harbored mutations in KIT, BRAF, or NRAS in their tumors, as shown in Table 2. The mutations were found in a mutually exclusive pattern, with the exception of 1 patient who had coexistent KIT P577S and NRAS Q61K mutations. 9 of 10 KIT mutations affected exon 11, the most frequently mutated KIT exon in GISTs as well as melanomas (ref. 3; Table 3). 2 patients, both with vulvar primaries, had exon 11 L576P mutations, the mutation site most frequently reported in melanoma (5, 6). 2 of the mutations found, L576P and V559, are frequent in GISTs (13). 1 KIT mutation was found in exon 13 (E635G) in an acral melanoma.

Consistent with previous reports (1), mucosal primaries had significantly fewer BRAF mutations than the 2 other groups (P < 0.01). Only 1 mucosal melanoma had a BRAF mutation (V600K). GNAQ mutations, which are common in uveal melanomas (14, 15), were not seen in any patient in our study. NRAS mutations were more common in acral than mucosal melanomas, but the difference was of borderline significance (P = 0.058). Overall our 14% incidence

Table 2. Number of tumors with mutations in KIT, BRAF, NRAS, or GNA by primary tumor type

<table>
<thead>
<tr>
<th>Primary site</th>
<th>N</th>
<th>KIT, n (%)</th>
<th>BRAF, n (%)</th>
<th>NRAS, n (%)</th>
<th>GNAQ (n)</th>
<th>Wild-type (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acral</td>
<td>22</td>
<td>3 (14)</td>
<td>7 (32)</td>
<td>6 (27)</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Mucosal</td>
<td>30</td>
<td>5 (17)</td>
<td>1 (3)</td>
<td>2 (7)</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>CSDS</td>
<td>38</td>
<td>2 (5)</td>
<td>13 (34)</td>
<td>5 (13)</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Totals</td>
<td>90</td>
<td>10 (11)</td>
<td>21 (23)</td>
<td>13 (14)</td>
<td>0</td>
<td>47</td>
</tr>
</tbody>
</table>

NOTE: Patient #45 had concurrent KIT and NRAS mutations.

Table 3. Characteristics and treatment responses of patients with KIT mutations and patients without KIT mutations treated with sunitinib

<table>
<thead>
<tr>
<th>ID#</th>
<th>Primary site</th>
<th>Mutation and exon</th>
<th>FISH⁺</th>
<th>CD117⁺ (3⁺ or 4⁺)</th>
<th>KIT allelic ratioᵃ</th>
<th>Treated with sunitinib</th>
<th>% Response and response durationᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>Acral</td>
<td>KIT 13 E635G</td>
<td>N/T</td>
<td>No</td>
<td>2:1</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Rectal</td>
<td>KIT 11 W557G</td>
<td>Yes</td>
<td>Yes</td>
<td>1:0</td>
<td>Yes</td>
<td>PR (85%) and 7 mo</td>
</tr>
<tr>
<td>34</td>
<td>Nasal</td>
<td>KIT 11G565V</td>
<td>No</td>
<td>Yes</td>
<td>1:1</td>
<td>Yes</td>
<td>PD</td>
</tr>
<tr>
<td>44</td>
<td>Scalp</td>
<td>KIT 11 P577S and NRAS 2 Q61K</td>
<td>No</td>
<td>Yes</td>
<td>1:1</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>Rectal</td>
<td>KIT 11 V559G</td>
<td>Yes</td>
<td>Yes</td>
<td>1:1</td>
<td>Yes</td>
<td>Not evaluable and 8-d therapy</td>
</tr>
<tr>
<td>64</td>
<td>Acral</td>
<td>KIT 11L576P</td>
<td>No</td>
<td>Yes</td>
<td>3:1</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>Vulva</td>
<td>KIT 11L576P</td>
<td>Yes</td>
<td>Yes</td>
<td>1:1</td>
<td>Yes</td>
<td>CR (100%) and 15 mo</td>
</tr>
<tr>
<td>75</td>
<td>Vulva</td>
<td>KIT 11L576P</td>
<td>Yes</td>
<td>Yes</td>
<td>1:0</td>
<td>Yes</td>
<td>PR (40%) and 1 mo</td>
</tr>
<tr>
<td>81</td>
<td>Scalp</td>
<td>KIT 11 V450D</td>
<td>No</td>
<td>Yes</td>
<td>1:1</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>82</td>
<td>Acral</td>
<td>KIT 11W557R and G565E</td>
<td>No</td>
<td>Yes</td>
<td>1:1</td>
<td>Yes</td>
<td>Not evaluable toxicity</td>
</tr>
<tr>
<td>6</td>
<td>Acral</td>
<td>BRAF V600E</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
<td>Yes</td>
<td>Stable and 4 mo</td>
</tr>
<tr>
<td>24</td>
<td>CSDS</td>
<td>BRAF V600E</td>
<td>No</td>
<td>Yes</td>
<td>N/A</td>
<td>Yes</td>
<td>PD</td>
</tr>
<tr>
<td>25</td>
<td>Acral</td>
<td>BRAF V600E</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>Yes</td>
<td>PD</td>
</tr>
<tr>
<td>39</td>
<td>Oral</td>
<td>NRAS 2 T11A</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>Yes</td>
<td>PD</td>
</tr>
<tr>
<td>52</td>
<td>Vulva</td>
<td>Wild-type</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
<td>Yes</td>
<td>PD</td>
</tr>
<tr>
<td>57</td>
<td>CSDS</td>
<td>Wild-type</td>
<td>No</td>
<td>Yes</td>
<td>N/A</td>
<td>Yes</td>
<td>PR (42%) and 1 month unconfirmed</td>
</tr>
</tbody>
</table>

NOTE: Patient 44 had a concurrent NRAS mutation Q61K and patient 75 died of cerebral hemorrhage before response confirmed. Abbreviations: FISH⁺, KIT amplification; CD117⁺ (3⁺ or 4⁺), immunohistochemistry positive for KIT protein; N/A, not applicable; N/T, not tested; PD, progressive disease.

ᵃAllelic ratio indicates the ratio of mutant to wild-type KIT sequence from the electropherogram, a marker previously found to be predictive of response to imatinib in patients with functionally uncharacterized KIT mutations.

ᵇPercent (%) response is maximum shrinkage of target lesions.
of NRAS mutations was similar to other studies of cutaneous melanoma. The NRAS mutations were found at codons 11 (n = 1), 12 (n = 5), and 61 (n = 7). There were 6 NRAS Q61R mutations.

The immunohistochemical assay using the CD117 antibody to assess KIT overexpression was positive in 27 of 86 patients tested (31%; Table 4). Although 8 of the 10 KIT mutated cases expressed high or very high levels of CD117, the other 2 mutant cases were negative based on the criteria for positivity. Conversely, KIT protein was overexpressed in 25% of cases without other KIT alterations and 70% of the cases with KIT overexpression did not show mutations of KIT. The FISH analysis showed copy number increase of KIT in 15 of 82 patients tested (18%), 4 of which had detectable KIT mutations.

Clinical results

Of the 90 patients screened, 30 were found to be eligible for sunitinib therapy based on the molecular analyses outlined above, of which 12 patients initiated therapy. Ten of these 12 patients were evaluable for response, with 1 complete response (CR), 3 partial responses (PR; 1 confirmed), 1 stable disease, and 5 patients with progressive disease. All 4 responses were seen within 6 weeks of starting sunitinib. 4 of the 10 evaluable patients were enrolled because of KIT mutation, 4 because of KIT amplification, and 2 because of KIT overexpression based on immunohistochemistry. Among the 4 evaluable patients with KIT mutations, 1 patient who had liver metastases had a complete remission for 15-month duration, 2 patients had partial remissions (1 confirmed), 1 stable disease, and 5 patients with progressive disease. All 4 responses were seen within 6 weeks of starting sunitinib. 4 of the 10 evaluable patients were enrolled because of KIT mutation, 4 because of KIT amplification, and 2 because of KIT overexpression based on immunohistochemistry. Among the 4 evaluable patients with KIT mutations, 1 patient who had liver metastases had a complete remission for 15-month duration, 2 patients had partial remissions (1 confirmed), and the remaining patient had disease progression (Table 2). Figure 1 shows the complete response of liver metastases in a patient with a vulvar primary and KIT exon 11 L576P mutation. The patient with the unconfirmed response died of a cerebral hemorrhage. Of the 4 patients enrolled because of KIT amplification, 1 had stable disease for 4 months whereas the other 3 progressed without response. Of the remaining 2 patients on trial who were enrolled because of KIT overexpression by immunohistochemistry, 1 had an unconfirmed partial response of 2-month duration and the other had progressive disease. 3 patients with KIT mutation were not treated with sunitinib because of death from melanoma or the development of multiple brain metastases whereas molecular testing was being conducted and 1 patient chose alternative therapy. Fourteen patients with KIT amplification or KIT overexpression without mutation were not treated with sunitinib because of clinical deterioration before obtaining results of KIT analysis in 2 patients and physician preference for alternate therapy in 12 patients. 1 patient, no. 82, developed congestive heart failure, possibly due to sunitinib, after 10 days of treatment and was taken off therapy. The tolerability and toxicity of sunitinib in the other 11 patients was similar to that reported in renal cell cancer and GISTs, with 5 of 12 patients requiring dose reductions of sunitinib.

1 of the 2 partial responders had a rectal melanoma and the mutational analysis of the initial biopsy of his 3-cm primary before treatment revealed a W557C KIT mutation and no detectable mutations in NRAS or BRAF. After a partial response to sunitinib of 7-month duration, he developed disease progression at both the primary site and the regional lymph nodes, and mutational analysis on his primary tumor resected at that time showed, in addition to the previously detected KIT mutation, a previously undetected NRAS Q61K mutation. Subsequent treatment with imatinib was ineffective.

In our exploratory survival analysis, we limited the patient population to the 79 patients with overt unresectable stage IV disease, thus excluding the 11 patients with...
stage III or resected stage IV disease who were expected to have a much better prognosis. Unfortunately, we did not have the date of onset of metastatic disease as a starting date but used the available date of consent for molecular testing as the starting date for survival analysis. This analysis included 9 patients with KIT mutations, 20 with BRAF, 7 with RAS, and 43 wild-type. Remarkably, this analysis showed a significantly worse prognosis for patients with KIT mutations compared with patients without KIT mutations (Fig. 2; \( P < 0.0001 \), log-rank test). Median survival was only 6 months for patients with KIT mutations, compared with 13 months for BRAF, 16 months for NRAS, and 17 months for patients wild type for the mutations tested. This difference remains significant even if the 1 patient with a KIT mutation and stage III disease is included in the analysis. The single patient with mutations in both KIT and stage III disease is included in the analysis.

Discussion

Our results confirm the previous anecdotal report of clinically significant responses of patients with melanoma with KIT mutations to therapy with sunitinib (16). Unfortunately, 2 of our patients received less than 2 weeks of therapy due to toxicity or rapid progression, but of the other 4 patients with KIT mutations, 3 had responses, including 1 complete response for 15 months and 1 unconfirmed partial response. This suggests that sunitinib has considerable more activity in patients with KIT mutations than in unselected patients with melanoma, where the response rate was only 8% (17). 2 of our responders had the L576P mutation, which also appears sensitive to imatinib (11). The few patients we treated with KIT amplification or overexpression based on CD117-positive staining but no KIT mutations were insufficient to give an indication whether sunitinib may be useful in these patient populations. A weakness of our study is the lack of central pathology review, particularly of CSDS cases. Our study confirms previous findings (5, 18) of a weak correlation of KIT overexpression by immunohistochemistry with KIT mutations but also shows that KIT immunohistochemistry is not sensitive or specific enough to reliably predict mutation status. Our finding of KIT mutations in 5% of patients with CSDS is lower than the 28% originally reported by Curtin and colleagues (1) but not statistically significantly higher than the recent report from Australia (ref. 19; \( P = 0.27 \), Fisher’s exact test).

Comparisons of sunitinib with other KIT inhibitors in the treatment of melanoma are fraught with hazard due to the small number of patients that have been reported with each agent. Carvajal and colleagues recently reported a multi-institutional trial of imatinib therapy for patients with melanoma with KIT aberrations and observed 6 responses (4 durable) in 25 evaluable patients (11), with 4 responses...
in 21 patients with KIT mutations. Guo and colleagues (10) observed 9 responses in 41 evaluable patients (22%) in their series. Given the modest response rate to imatinib in this patient population, our observation of 3 responses in 4 evaluable patients suggests that the activity of sunitinib may be at least comparable with imatinib. Interestingly, the median age of patients in both our series and the study by Carvajal and colleagues was more than 70 years. While BRAF mutations are more common in young patients with melanoma, our data suggest that KIT mutations may be more prevalent in older patients. Dasatinib has also been reported to produce responses in a few cases. Although some in vitro studies have favored dasatinib (20), sunitinib may have an advantage over other KIT inhibitors given its antiangiogenic activity through the inhibition of VEGFR1, VEGFR2, VEGFR3, and platelet—derived growth factor receptor (PDGFR). Several phase II studies have shown the activity of other angiogenesis inhibitors in the treatment of unselected patients with metastatic melanoma (21, 22). Although the data in GISTs suggest that sunitinib is more effective against patients with exon 9 than in exon 11 mutations, we observed responses in 2 of 3 evaluable patients with exon 11 mutations. Although almost all of the patients in the study of Carvajal and colleagues who responded to imatinib had a KIT allelic ratio greater than 1, we observed 1 complete response and 1 case of progressive disease in 2 evaluable patients with an allelic ratio of 1.

In 1 patient who had a partial response to therapy, the resistance progression was associated with the appearance of a previously undetected mutation in the NRAS gene. This result may be due to genetic heterogeneity in the initial primary tumor, technical factors, or the development of a secondary mutation as a consequence of therapy with sunitinib. As this mutation is expected to lead to activation of the mitogen-activated protein kinase (MAPK) pathway and phosphoinositide 3-kinase (PI3K) pathway downstream of KIT, it is expected to bypass any inhibition of these pathways mediated by pharmacologic inhibition at the level of the upstream receptor KIT. A recent analysis of patients who developed resistance to the BRAF inhibitor vemurafenib (PLX4032) also found NRAS mutation as 1 mechanism of resistance to a BRAF inhibitor (23). While resistance to targeted therapy in chronic myelogenous leukemia is usually related to new mutations in the targeted BCR-ABL gene, resistance to targeted therapy in melanoma appears in some cases to be related to tumor cell acquisition of new mutations in other genes that contribute to tumor growth.

Our exploratory survival analysis suggests that the presence of a KIT mutation is an adverse prognostic factor for patients with melanoma; a similar observation has recently been made in a Chinese population of patients with melanoma (24). Because patients with KIT mutations have a short survival, it will be important to determine their mutation status earlier during the course of the disease, to avoid any delays once the disease becomes widely metastatic. Because KIT and BRAF mutations appear in a mostly mutually exclusive pattern, and given the higher prevalence of BRAF mutations in most melanoma subtypes, a practical algorithm might be to first test melanomas for BRAF mutations, then assess KIT status in patients with mucosal, acral, and CSDS melanomas that did not have BRAF mutations. It has been estimated that 1.3% of patients with melanoma in the United States have mucosal primaries (25); if 17% have KIT mutations, there are less than 200 stage IV patients with KIT-mutated mucosal primaries in the United States per year. Our study illustrates the difficulties that beset a study of rare tumors such as KIT-mutated melanoma: although effective therapy may be available, it is difficult to identify sufficient patients for a systematic study. Scenarios such as this 1 may necessitate a new regulatory pathway for drug approval as even a modest sized phase II or III trial may be impossible to complete in a reasonable time frame. Most notably a multicenter International randomized phase III trial of nilotinib was started in this patient population in 2010 (ClinicalTrials.gov NCT01028222), but despite opening the trial at 83 centers, the difficulty of finding eligible patients necessitated converting the trial to a single-arm phase II study (Novartis, personal communication).

Our finding of responses to sunitinib in KIT-mutated patients with melanoma requires confirmation in a larger cohort. In addition, because of the poor prognosis of patients with mucosal melanoma treated with conventional therapy, a prospective study of a KIT inhibitor as a surgical adjuvant, given either preoperative or postoperative, appears appropriate for patients with mucosal melanoma with KIT mutations. Use of KIT inhibitors, such as sunitinib, in patients with melanoma and KIT mutations represents a successful example of personalized oncology with the use of tumor mutational status to direct therapy.

Disclosure of Potential Conflicts of Interest
The manuscript represents an original clinical trial. D.R. Minor and B.C. Bastian receive research support from Pfizer and B.C. Bastian is a consultant for Novartis and receives honoraria from Novartis. No potential conflicts of interest were disclosed by other authors.

Authors’ Contributions
D.R. Minor contributed to the literature search and figures.
D.R. Minor and B.C. Bastian contributed to the study design.
D.R. Minor, B.C. Bastian, M. Kashani-Sabet, and M. Carido contributed to the data analysis and interpretation and writing.
All authors contributed to the data collection and approved the final manuscript.

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References

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