Activity of Sorafenib against Desmoid Tumor/Deep Fibromatosis

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Abstract

Background: Desmoid tumors (deep fibromatoses) are clonal connective tissue malignancies that do not metastasize, but have a significant risk of local recurrence, and are associated with morbidity and occasionally mortality. Responses of desmoid patients to sorafenib on an expanded access program led us to review our experience.

Methods: After Institutional Review Board (IRB) approval, we reviewed data for 26 patients with desmoid tumors treated with sorafenib. Sorafenib was administered at 400 mg oral daily and adjusted for toxicity.

Results: Sorafenib was the first-line therapy in 11/26 patients and the remaining 15/26 had received a median of 2 prior lines of therapy. Twenty-three of 26 patients had shown evidence of progressive disease by imaging, whereas 3 patients had achieved maximum benefit or toxicity with chemotherapy. Sixteen of 22 (70%) patients reported significant improvement of symptoms. At a median of 6 months (2–29) of treatment, the best response evaluation criteria in solid tumors (RECIST) 1.1 response included 6/24 (25%) patients with partial response (PR), 17/24 (70%) with stable disease, and 1 with progression and death. Twelve of 13 (92%) patients evaluated by MRI had >30% decrease in T2 signal intensity, an indirect metric for increased fibrosis and loss of cellularity. Eighty percent of patients with radiological benefit had extra-abdominal desmoids.

Discussion: Sorafenib is active against desmoid tumors. A prospective, randomized clinical trial of sorafenib against other active agents is warranted. Loss of MRI T2 signal may be a useful surrogate for defining responses, but requires validation by examination of tumor pathology.

Introduction

Desmoid tumors, also known as deep fibromatoses (DT/DF), are fibroblastic neoplasms that arise from musculo-poneurotic stromal elements (1), containing small bundles of spindle cells with rare mitoses in an abundant stroma. DT/DF arises most commonly in the extremity, abdominal cavity (root of the mesentery), retroperitoneum, and abdominal wall (2). DT/DF are often considered benign due to their lack of metastatic potential. However, DT/DF cause significant morbidity by infiltrating or exerting mass effects on vital structures (3, 4). Mortality from DT/DF is occasionally observed owing to the local aggressiveness of some tumors, typically in the mesentery (4).

If DT/DF remain indolent, they may be observed (3, 4). For patients with symptoms or progressive disease, primary treatment is surgical resection with wide margins. Radiation therapy (RT) is used in some patients with high-risk features, or in recurrent or surgically unresectable disease (5, 6). Morbidity from multimodal treatments remains high. Based on case reports and small series, nonsteroidal anti-inflammatory agents and antiestrogens are employed when surgery and radiation are unable to achieve local control. DT/DF have variable expression of estrogen receptor alpha (ER) and uniform expression of ER-β; however, receptor status does not correlate with clinical outcome (7).

Cytotoxic chemotherapy is usually reserved for symptomatic or progressive disease not amenable to surgery or radiation (8, 9). Anthracyclines are active when used as single agents or in combinations (10–12). Other active systemic regimens include vinca alkaloid-methotrexate combinations (13), single agent dacarbazine or temozolomide or combinations employing more than one of these agents. In our previously published series, hormonal therapy and anthracyclines (typically pegylated liposomal doxorubicin) were the most effective regimens, whereas other agents were less effective (8, 9).
Translational Relevance

Desmoid tumors are monoclonal neoplasms that harbor mutations in CTNNB1 or APC. The presence of KIT or platelet-derived growth factor receptors (PDGFR) in desmoid tumors led to clinical trials with imatinib with cumulative response evaluation criteria in solid tumors (RECIST) response rate < 10%. There are no imaging or biomarkers that predict natural history or clinical benefit with systemic therapy for desmoid tumors. We show that sorafenib, a multitargeted kinase inhibitor, results in shrinkage and symptom relief to a degree not seen with imatinib. The loss of T2 signal intensity by contrast enhanced MRI, which seems to be related to loss of tumor viability, may be a novel radiological marker for response in this disease. We believe that sorafenib represents a novel, practice changing therapy that can circumvent mutilating surgery or amputation in this population.

Kinase directed therapy has also been employed against desmoids tumors. In a Phase II study with imatinib, 3 partial responses (PR) in 51 patients (6%) were observed after 18 or more months of treatment (14). The response rate was lower than that from smaller multicenter studies (15, 16). Sorafenib (BAY-43–9006) is a multitargeted oral tyrosine kinase inhibitor. After we observed DT/DF patients who received sorafenib through an expanded access program who attained clinical and radiological benefit [response evaluation criteria in solid tumors (RECIST) PR and loss of MRI T2 signal intensity], we retrospectively assessed our experience with sorafenib in DT/DF patients.

Methods

Patient selection

Following institutional IRB approval (waiver WA0209–04), we identified and reviewed medical records of 26 patients from February, 2008 to October, 2010 who received sorafenib for DT/DF in our clinic. We collected the following data: age at the date of diagnosis, presentation status (primary or recurrent), gender, presence of Gardner syndrome, primary site, primary size, radiological appearance (diffuse versus nodular), number and type of surgeries, use of radiation therapy, lines, duration and response on prior therapies (hormonal, cytotoxic, and tyrosine kinase inhibitors), reason for treatment discontinuation, time to progression, documentation of progression before initiation of sorafenib, dose and toxicities of sorafenib, overall survival, and status.

Imaging techniques

Radiological measurements were made by a single board certified radiologist (R.A.L.) with experience of evaluating soft tissue tumors by MRI or CT. The radiologist was blinded to patient treatment. Modalities employed in evaluating this heterogeneous group of patients include: (i) MRI with gadolinium for tumors of the extremities, chest wall, or neck (13 patients, 52 scans), (ii) CT with intravenous contrast (7 patients, 26 scans) or oral contrast only (4 patients, 13 scans) for tumors involving mesentery, abdominal wall, or thorax.

T2-weighted MRI values were assessed by two methods. In the first method, the radiologist drew the largest electronic Region of Interest (ROI) staying within the boundaries of each tumor at its greatest cross-sectional diameter and calculated a ratio between this value (C1) and adjacent skeletal muscle (M1). These measurements were repeated at the same location of the tumor and adjacent muscle on subsequent post-treatment examinations (C2 and M2, respectively). A normalized decrease of T2 signal intensity of 30% [i.e., (C2/M2)/(C1/M1)] was arbitrarily defined as significant. In the second method, the same radiologist visually estimated the percentage of the entire tumor on all sections that was darker than muscle on T2 weighted images, in 10% increments (0–100%); this estimate was repeated for all follow-up studies.

Role of the funding source

Grant and philanthropic support was used to support the costs of the collection and analysis of data in this retrospective analysis.

Results

Patient characteristics

The study population is summarized in Table 1. There were 17 females and 9 males in this cohort. Median age at diagnosis and presentation was 29.5 years (range 17–57) and 31 years (range 20–59), respectively. At initial diagnosis, 16 patients underwent surgical resection and 10 patients had surgically unresectable disease, or disease only resectable by amputation. At the time of presentation, all 26 patients had unresectable disease or disease only removable by amputation (7 with multifocal disease). Seven patients had antecedent surgery and developed DT/DF at the surgical site within a median of 36 months (range 12–132); 4 of 7 had a history of familial adenomatous polyposis (FAP) and underwent prophylactic colectomy. Three of 7 (non-FAP) patients had hemicolectomy for rectal adenocarcinoma, node dissection for invasive breast cancer, and breast implant for congenital breast hypoplasia. One patient had pregnancy-associated DT/DF.

Tumor characteristics

The histological diagnosis was confirmed at our institution in 24/26 patients. Primary sites included: abdomen/pelvis (12), extremity (6), trunk/chest wall (6), and head and neck (2). Radiological appearance of the tumor was nodular (6) or diffuse/infiltrative (20). The primary tumor size was <5 cm (4), 5–10 cm, (11) and >10 cm (11).

Treatment characteristics

Local therapy. At initial diagnosis, sixteen patients underwent surgery for resectable disease. Median time to
recurrence after surgery was 24 months (range 1–120). Three patients underwent a second surgery at recurrence and subsequently had unreatable disease after 10, 24, and 36 months. Four of 26 patients received adjuvant radiation following primary resection. One patient had adjuvant radiation and at recurrence had neo-adjuvant radiation to the same site followed by adjuvant brachytherapy. One patient received adjuvant breast radiation for breast cancer; the DT/DF was found in the axilla following an axillary dissection.

**Systemic therapy.** We do not report the use of nonsteroidal anti-inflammatory agents due to poor documentation, inability to evaluate compliance, and the recognized low response rate. Prior systemic therapy included hormonal manipulation, chemotherapy, and tyrosine kinase inhibitors. Fifteen of 26 patients received a median of 2 prior systemic treatments (range 1–5), whereas 11 of 26 patients had sorafenib as first-line treatment. Of the 15 patients who received prior systemic therapy, 8 received hormonal therapy for a median of 8 months (range 1–35) with tamoxifen (6), leuprolide (1), and medroxyprogesterone (1) before progression. Best response to hormonal treatment included stable disease and a minor response in a single patient after 6 months of therapy. Eleven of 15 patients received a median of 2 lines (range 1–3) of cytotoxic chemotherapy for a median of 7 months (range 3–42), consisting of single agents or combinations involving doxorubicin (4), liposomal pegylated doxorubicin (8), dacarbazine (DTIC) (4), methotrexate (2), and cyclophosphamide (2). Best response to chemotherapy included 4 patients with minor response and 5 patients with SD. Of these, four patients experienced long periods of observation (26, 42, 44, and 84 months) following doxorubicin or liposomal pegylated

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**Table 1. Characteristics of 26 patients on study**

<table>
<thead>
<tr>
<th>Patient and tumor characteristics</th>
<th>Prior treatment characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Patients</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>29.5</td>
</tr>
<tr>
<td>At presentation</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>12</td>
</tr>
<tr>
<td>Extremity</td>
<td>6</td>
</tr>
<tr>
<td>Trunk/Chest wall</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Characteristics (radiological)</td>
<td></td>
</tr>
<tr>
<td>Multifocal</td>
<td>7</td>
</tr>
<tr>
<td>Diffuse</td>
<td>20</td>
</tr>
<tr>
<td>Nodular</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td></td>
</tr>
<tr>
<td>≤5 cm (T1)</td>
<td>4</td>
</tr>
<tr>
<td>5–10 cm (T2)</td>
<td>11</td>
</tr>
<tr>
<td>&gt;10 cm (T3)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>FAP</td>
<td>4</td>
</tr>
<tr>
<td>Prior surgeryc</td>
<td>7</td>
</tr>
<tr>
<td>Surgery for FAP</td>
<td>4/7</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery for other</td>
<td>3/7</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aSD: Stable Disease by RECIST. 
bMinor response: decrease by 10% to 29% by RECIST criteria. 
cSurgery for other reasons before diagnosis of desmoid.
doxorubicin administered for a median of 20 cycles (~20 months). Toxicity with anthracyclines included congestive heart failure, alveolar bone loss in the jaw, mucositis, alopecia, and fatigue. Tyrosine kinase inhibitors other than sorafenib had been employed in 6/14 patients for a median of 3 months (range 1–7) with 1 patient intolerant of the drug, 4 patients with disease progression, and 1 patient with minor radiologic response as best outcome.

**Sorafenib administration.** Sorafenib was initiated when progression was noted on imaging in 23/26 patients; 3 patients had Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST) stable disease on chemotherapy, but experienced worsening pain. Sorafenib was started in 15/26 patients after a median of 2 lines of prior systemic therapy administered for a median of 5 months. Sorafenib was initiated as first-line therapy in 11/26 patients after a median of 13 months (range 2–42) from diagnosis. At the time of this report, first- and second-line patients received sorafenib for a median of 4.6 (1–31) and 12 (2–26) months, respectively. Sorafenib was first line in 20% and 40% of patients with abdominal and extra-abdominal tumors, respectively. Sorafenib was started at a maximum dose of 400 mg daily and decreased for toxicity. No patient was treated at 400 mg twice daily; the dose approved in renal cell or hepatocellular carcinoma. The median dose of sorafenib was 200 mg daily. Some patients required further dose reductions to 200 mg every other day, whereas others tolerated alternating doses of 400 mg and 200 mg daily (300 mg/day). Toxicities are described in Table 2 and tolerated alternating doses of 400 mg and 200 mg daily (300 mg/day). Toxicities are described in Table 2 and include hand-foot syndrome, fatigue, skin rash, trichodynia, hypertension, mild alopecia, and diarrhea. Side effects were well controlled with dose adjustments and inclusion of antidiarrhea and antihypertensive drugs.

**Clinical outcome on sorafenib**

Clinical outcome of sorafenib therapy is detailed in Table 2 along with duration, type of response, and drug toxicities. Median follow up on sorafenib was 6 months (range: 2–29). Sixteen of 22 (~70%) patients reported subjective decrease in pain and analgesic use after initiation of sorafenib; these data were not quantitated with a validated pain scale. Some examples of clinical benefit include (i) a 21-year-old-male (Table 2, Pt 1, and Fig. 1) who had tumor extending from axilla to brachial artery, median, and ulnar nerve which resulted in pain, swelling, and loss of mobility. Forequarter amputation remained the only option to render the patient disease-free. Within 2 months of sorafenib the patient experienced a RECIST PR and complete resolution of symptoms; (ii) a 24-year-old-female (Table 2, Pt 15) had a large desmoid tumor displacing her mediastinum and impeding cardiopulmonary collapse despite other therapy. Within one week of sorafenib she had dramatic improvement in orthopnea, dyspnea, and lower extremity edema; (iii) a 21-year-old-woman (Table 2, Pt 9) with inoperable cervical spine mass presented with pain and compromised mobility. Therapy did not result in change in tumor size; however, there was loss of T2 signal and pain relief. Notably, no symptomatic benefit was reported by patients with intra-abdominal desmoids. Three patients stopped sorafenib within 2 months due to abdominal pain, uncontrolled hypertension, or visual disturbances. Neither cardiac toxicity nor bleeding was observed.

**Reinstitution of therapy**

A patient was treated for 18 months and experienced a RECIST PR and clinical benefit. Following 6 months of observation she experienced local progression. Restarting sorafenib resulted in pain relief and tumor shrinking. Similar findings have been noted in two other patients, raising the question of response durability after treatment discontinuation.

Another patient attained SD with sorafenib after progressing on several lines of chemotherapy. Sorafenib was switched to sunitinib due to toxicity, resulting in disease progression. Reinitiation of sorafenib resulted in pain relief and disease stabilization.

**Radiological response assessment**

**RECIST 1.1.** Twenty-four of 26 patients were evaluable for response. CT or MRI was obtained at a median interval of 4 months. Responses by RECIST 1.1 were as follows: 6 of 14, complete responses; 6 of 24, partial responses (25%); 17 of 24 (70%), stable disease; and 1 patient with progressive disease. Seven patients experienced minor response (defined as 10%–29% decrease). Figure 2 depicts RECIST responses in 24 evaluable patients. Bidimensional WHO size measurements were highly correlated ($R^2 = 0.92$) with RECIST ($r = -0.97$, Student’s t test). RECIST PR was achieved at a median of 10 months and a minor response (i.e., reduction > 10% by RECIST) was noted at a median of 4 months of starting therapy. PR and SD were mostly seen in extra-abdominal tumors ($P = 0.03$, Student’s t test) and there was no difference in between those who received sorafenib as first-line or second-line ($P = 0.9$, Student’s t test).

**MRI signal changes**

13 patients were evaluable by MRI (Fig. 3). T2 signal changes were quantitatively and qualitatively described (see Methods). We defined a 30% loss of T2 signal relative to muscle as a response. We anecdotally noted that patients with changes in T2 signal had described symptomatic improvement; however, this was not correlated with a formal quality of life scale. T2 changes were seen in 12 of 13 (~90%) patients who had an MRI. T2 signal change was seen in 100% of patients with a RECIST PR. Median time to T2 signal loss (> 30%) was 5 months for those who obtained a PR (median 47% decrease) and 3.6 months for those achieving SD as best result. In this small data set, the sensitivity and specificity of T2 signal loss as a predictor of RECIST PR was 100% and 12%, respectively. T2 signal loss has a positive predictive value and negative predictive value of 42% and 100%, respectively.

**Survival**

The 26 patients were followed for a median of 50 months (3–209 months) from initial diagnosis. Median follow-up...
<table>
<thead>
<tr>
<th>Pt</th>
<th>Location</th>
<th>Initial symptoms</th>
<th>Clinical benefit on sorafenib</th>
<th>Best RECIST response to sorafenib</th>
<th>Best T2 MRI signal change (from baseline)</th>
<th>Visual approximation of &quot;darker than muscle.&quot;</th>
<th>Sorafenib toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 (P)</td>
<td>UE</td>
<td>Pain and discomfort at tumor site. Fore-quarter amputation only option.</td>
<td>Complete resolution of symptoms in 2 mo (partial relief within 1 wk).</td>
<td>-42%</td>
<td>-47%</td>
<td>80%</td>
<td>Fatigue (gr 1), HF (gr 2), diarrhea (gr 1), and easy bruisingability. All unresolved.</td>
</tr>
<tr>
<td>02 (F)</td>
<td>H&amp;N</td>
<td>Pain and compromised ROM of neck.</td>
<td>Some improvement in 4 mo, complete resolution in 15 mo.</td>
<td>-42%</td>
<td>-35%</td>
<td>90%</td>
<td>Fatigue (gr 3), HF (gr 2), GI (gr 1): all resolved completely.</td>
</tr>
<tr>
<td>03 (F)</td>
<td>LE</td>
<td>Difficult to walk due to pain.</td>
<td>Complete resolution of symptoms.</td>
<td>-40%</td>
<td>-47%</td>
<td>50%</td>
<td>Diarrhea (gr 1): resolved. Mild alopecia, Diarrhea (gr 2), HF (gr 2): unresolved.</td>
</tr>
<tr>
<td>04 (F)</td>
<td>CW/T</td>
<td>Shooting pain and L-ROM.</td>
<td>Significant decrease within 1 mo. Improved ROM.</td>
<td>-36%</td>
<td>-90%</td>
<td>90%</td>
<td>Occasional diarrhea, HF (resolving).</td>
</tr>
<tr>
<td>05 (P)</td>
<td>UE</td>
<td>Pain and swelling. Limited ROM.</td>
<td>Mild improvement after 12 months.</td>
<td>-31%</td>
<td>-80%</td>
<td>90%</td>
<td>Hypersensitivity and rash of soles/scalp: resolved.</td>
</tr>
<tr>
<td>06 (P)</td>
<td>UE</td>
<td>Pain, fullness, and limited ROM.</td>
<td>Significant improvement in all symptoms in 2 wks.</td>
<td>-28%</td>
<td>-40%</td>
<td>30%</td>
<td>HF: Grade 2 (resolved to Gr 1). Mild alopecia.</td>
</tr>
<tr>
<td>07 (P)</td>
<td>LE</td>
<td>Swelling of entire leg and difficulty ambulating. Pruritus at tumor site.</td>
<td>Significant decrease in swelling and improved ambulation.</td>
<td>-27%</td>
<td>-60%</td>
<td>50%</td>
<td>No pruritus.</td>
</tr>
<tr>
<td>08 (F)</td>
<td>CW/T</td>
<td>Pain requiring narcotics.</td>
<td>Significant decrease in pain and softer mass. Off narcotics.</td>
<td>-15%</td>
<td>-45%</td>
<td>30%</td>
<td>Rash and HTN: resolved.</td>
</tr>
<tr>
<td>09 (P)</td>
<td>H&amp;N</td>
<td>Pain in neck.</td>
<td>Pain and ROM improved within 1 week.</td>
<td>-13%</td>
<td>-30%</td>
<td>20%</td>
<td>HF (gr 2), HTN (gr 2) and slight alopecia: all resolved.</td>
</tr>
<tr>
<td>10 (P)</td>
<td>UE</td>
<td>Tightness over axilla and pain.</td>
<td>Worsening pain on therapy.</td>
<td>-11%</td>
<td>-50%</td>
<td>60%</td>
<td>HF (gr 3, ongoing), fatigue, and rash: resolved.</td>
</tr>
<tr>
<td>11 (F)</td>
<td>RP/PS</td>
<td>Dull ache.</td>
<td>Mild improvement.</td>
<td>-3%</td>
<td>-57%</td>
<td>20%</td>
<td>Rash (gr 3), HF (gr 1): all improved.</td>
</tr>
<tr>
<td>12 (F)</td>
<td>UE</td>
<td>Significant pain and stiffness.</td>
<td>Significant decrease in 2 wks.</td>
<td>-1%</td>
<td>-5%</td>
<td>10%</td>
<td>Fatigue, H&amp;F syndrome, and fatigue (all resolved)</td>
</tr>
<tr>
<td>13 (P)</td>
<td>LE</td>
<td>Severe shooting pain in leg.</td>
<td>Slight decrease in pain.</td>
<td>+4%</td>
<td>-75%</td>
<td>90%</td>
<td>None</td>
</tr>
</tbody>
</table>

(Continued on the following page)
| Pt  | Location | Initial symptoms | Clinical benefit on sorafenib | Best RECIST response to sorafenib | Best T2 MRI signal change from baseline | Visual approximation of "darker than muscle."
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Abd/RP</td>
<td>No symptoms</td>
<td>No symptoms</td>
<td>−30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>CW/T</td>
<td>Dyspnea on exertion, sharp chest pain, edema, impending cardiopulmonary collapse.</td>
<td>Significant decrease in symptoms within 1 mo. Complete symptom resolution in 3 months.</td>
<td>−19%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Abd/RP</td>
<td>Diarrhea</td>
<td>Diarrhea resolved within 1 mo.</td>
<td>−19%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Abd/RP</td>
<td>Severe abdomen pain</td>
<td>Worse on treatment</td>
<td>−9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Abd/RP</td>
<td>Pain from hydronephrosis</td>
<td>Pain relief with ureteral stent.</td>
<td>−8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Abd/RP</td>
<td>No symptoms</td>
<td>No symptoms</td>
<td>−8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Abd/RP</td>
<td>Intermittent abdominal pain</td>
<td>Worsening of symptoms</td>
<td>−7%</td>
<td></td>
<td></td>
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<tr>
<td>21</td>
<td>Abd/RP</td>
<td>No symptoms</td>
<td>No symptoms</td>
<td>−3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Abd/RP</td>
<td>No symptoms</td>
<td>No symptoms</td>
<td>+11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Abd/RP</td>
<td>Abdominal pain, distension</td>
<td>Worsening pain. POD and death.</td>
<td>+17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Abd/RP</td>
<td>Intermittent abdominal fullness</td>
<td>No improvement in symptoms.</td>
<td>+18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Abd/RP</td>
<td>Abdominal fullness</td>
<td>Abdominal fullness</td>
<td>No scan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>RP/PS</td>
<td>Significant back pain</td>
<td>Immediate relief within 1 week.</td>
<td>No scan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: mo, months; L-ROM, Limited range of motion; LE, lower extremity; UE, upper extremity; CW/T, Chest wall or trunk; H&N, head and neck; Abd/RP, abdomen or retroperitoneum; Abd, abdominal; RP/PS, retroperitoneal and paraspinal; GI includes: nausea, vomiting and/or diarrhea; HF, Hand–Foot syndrome.

*aMethods section for calculation of signal decrease.

*bDecrease in T2 signal as estimated by a single radiologist blinded to treatment. FAP: familial adenomatous polyposis. (F) First line sorafenib, (P) Prior therapies.
from the start of sorafenib was 6 months (1–29). Median
time to progression was not reached. Five patients pro-
gressed despite sorafenib, defined as increasing tumor size
(2), symptoms (1), or drug intolerance (2). Twenty-five of
26 patients are alive with disease.

Discussion

DT/DF have a highly variable clinical presentation and
natural history. There are no standard first-line systemic
therapies in DT/DF as only few agents have been examined
 prospectively and there are no randomized studies. In this
cohort, median progression-free survival (PFS) rates were
not reached. Only one patient (with Gardner syndrome)
had progressive disease and died. Because desmoid tumors
may have a relatively indolent course, we submit that overt
radiological response rate and symptomatic improvement
may be better primary endpoints for outcome than PFS for
clinical trials. Any response must also take into account the
occasional patient with spontaneous regressions or delayed
regressions from prior therapy.

The most striking aspect of this study is the rapid
clinical benefit seen in 16 of 22 (~70%) of symptomatic
patients. Clinical improvement was typically noted
within 2 weeks of starting sorafenib; we had not observed
such clinical benefit with imatinib. It is notable that
radiological benefit (RECIST complete response + partial
response + stable disease rate [CR+PR+SD]) were most
common in extremity DT/DF rather than intra-abdom-
inal tumors (P = 0.03, t-test). There was no difference
in radiological benefit when sorafenib was first-line or
second-line treatment (P = 0.9). These findings suggest
that the response of DT/DF to sorafenib is a function of
their biology, i.e., APC mutation (Gardner syndrome) for
intra-abdominal desmoids (17, 18) versus β-catenin
mutation commonly observed in other DT/DF (19).
Conversely, it is difficult to ascribe antiangiogenic effects
of sorafenib as directly responsible for the observed
benefit. To date, there are no biomarkers that inform
natural outcome or clinical benefit with therapies. Tumor
or serum levels of KIT, PDGFR, PDGF-AA, PDGF-BB, and
CTNNB1 or APC mutation status have not correlated with

Figure 1. An MRI (with contrast,
T2 weighted) of the upper arm
depicting a desmoid tumor
encasing a neurovascular bundle
before (A) and after six months (B)
of sorafenib.

Figure 2. Waterfall plot of best radiological outcome by
size (RECIST 1.1) for individual patients along with
duration of response (months) and type of imaging noted
below each patient column.

Individual patients: 1–24

Maximum percent change from baseline of
target lesion diameter

= Intra-abdominal
responses to TKI therapy (14–16). Research is underway to elucidate why nonabdominal desmoids respond more frequently to sorafenib than mesenteric desmoids, which may also point to the potential durability of response once treatment has been interrupted.

The optimal imaging modality to evaluate DT/DF remains undefined. Six of 24 patients experienced a RECIST PR and 7 of 24 had minor tumor shrinkage (10%–29%) that represent a response using the alternative response criteria developed by Choi for gastrointestinal stromal tumors (20). Focusing more on the MRI characteristics of desmoids, studies that evaluated soft tissue tumors noted that differences in MRI characteristics are related to the ratio of fibroblasts to collagen (21). We observed that sorafenib leads to T2 signal loss in 12 of 13 (~90%) patients, which is suggestive of a shift in fibroblast to collagen ratio. T2 signal loss was observed in all patients with a RECIST PR. Whether T2 signal represents a biological effect is a question for prospective trials with endpoints evaluating quality of life, pre- and post-treatment pathology, and time to relapse.

Quantitating MRI T2 signal intensity may be a novel radiographic metric in DT/DF. Stacchiotti and colleagues showed that T1 signal on contrast enhanced MRI may be a novel radiologic marker of response in high-grade sarcomas treated with neoadjuvant chemotherapy/radiation (22). In contrast to computed tomography, in which Hounsfield units may be used as a metric of tissue density, in MRI T2 signal is a unitless number with no intrinsic meaning except for comparative purposes. In attempting to develop a reproducible metric for clinical improvement, we normalized the signal intensity of lesions by using normal muscle as a reference standard. In this analysis, MRI scans were not carried out with identical parameters, which are expected to cause variation in the measured T2 signal intensity, even with a reference standard. In addition, we used a region of interest (ROI) on one representative section, which introduces sampling error. In these patients, the changes in signal were homogenous when they did occur, and, thus, our measurements were arguably representative of the entire lesion.

The above limitations argue for a prospective study to further evaluate this metric.

Despite our attempt to capture all treated patients, the retrospective nature of this study exposes it to selection bias, as well as possible lead-time bias related to variable imaging intervals. Nonetheless, the relative rapidity of the clinical and radiological responses was striking and appeared to be in excess of what has been reported with other systemic agents, at least as pertains to desmoids not associated with Gardner syndrome. Our clinical observations are supportive of a prospective, randomized trial comparing sorafenib with other active agents, and hopefully provide an otherwise underappreciated means to manage disease in difficult anatomic locations.

Disclosure of Potential Conflicts of Interest

R.G. Maki has Commercial Research Grant (Pfizer, Hoffman LaRoche). D.R. D’Adamo has research grant from Bayer. R.G. Maki has honoraria from Speakers Bureau (Novartis, Ziopharm). R.G. Maki is a consultant/advisory board member of Bayer, Novartis, Eisai, and Lilly. R.G. Maki (NCI: CA148260, CA47179, CA140146; Philanthropy-Cycle for Survival).

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Authors’ Contributions

M.M. Gounder was responsible for conception, design, collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript; R.A. Lefkowitz collected and assembled the data, conducted data analysis and interpretation, manuscript writing, final approval of manuscript; M.L. Keohan, D.R. D’Adamo, M. Hameed, C.R. Antonescu, S. Singer, K. Stout, and L. Ahn were responsible for collection and assembly of data, data analysis and interpretation, final approval of manuscript; and R.G. Maki was responsible for conception, design, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript, administrative support, and financial support.

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Figure 3. Waterfall plot of best radiological outcome by size (RECIST 1.1) of patients evaluated by MRI, duration of response (months) and change in T2 signal intensity (gray columns).
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