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Scholarly Report Title: Effective Management of Desmoid Fibromatosis With Sorafenib in Children

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Abstract

Title: Effective Management of Desmoid Fibromatosis With Sorafenib in Children

Kinjan Parikh, Annette Werger, Carlos Rodriguez-Galindo, MD

Purpose: Desmoid fibromatosis is a locally aggressive neoplasm with high recurrence rate after surgery and no well-defined treatment guidelines. In this paper, we evaluate the effectiveness of sorafenib on tumor response.

Methods: We identified all pediatric patients with desmoid tumors treated with sorafenib in our institution. We then completed a thorough retrospective chart review and evaluated treatment response based on clinical changes. Descriptive statistics were used to determine efficacy of sorafenib.

Results: Four patients were studied. Sorafenib was dosed starting at 200mg daily and raised to 400mg daily. Median duration of treatment was 12 months. Side effects included fatigue, nausea, skin rash, hypertension, weight loss and neuropathy. In all patients, treatment with sorafenib resulted in significant clinical improvement within months of treatment and no evidence of disease progression from 2 to 13 months from discontinuation of therapy.

Conclusions: Based on the promising results on our patients, we conclude that sorafenib is active agent in desmoid fibromatosis and its use should be strongly considered in the first line treatment in cases of unresectable disease. However, further prospective studies should be conducted to further define the role of sorafenib in this treatment.
My Contribution:

As first author of this paper, I worked most closely with my mentor Dr. Carlos Rodriguez-Galindo. The paper originated when he described to me two new drugs being trialed on desmoid tumors, a notoriously stubborn tumor with no definitive treatment guidelines. We began to track tumor response to both hydroxyurea and sorafenib. I was responsible for obtaining approval from the IRB of the Dana-Farber/Harvard Cancer Center Office for Human Research Subjects. I subsequently generated a list of all the patients that had been treated at Dana Farber with these drugs, and I began my retrospective chart review. I made Excel spreadsheets and charts documenting details of the patients’ diagnoses, prior treatments, current treatments, and progress of the tumor over time. I documented side effects, relapses, and any other information deemed pertinent. Based on this, there appeared to be a significant effect on tumors with sorafenib while hydroxyurea did not have a clear benefit on tumor course. Together, we decided to focus on the effects of sorafenib alone. I continued to analyze the charts for clinical improvement as these patients were currently on treatment. I continued to compare symptomatic improvement, side effect profile, and change in tumor size over the time course of the treatment to assess effectiveness. We used descriptive statistics in our analysis, as our patient population was too small to do otherwise. I then compiled all of the data and created the first draft of our paper. The final draft was accomplished with edits from Dr. Rodriguez-Galindo.
APPENDIX

EFFECTIVE MANAGEMENT OF DESMOID FIBROMATOSIS WITH SORAFENIB IN CHILDREN

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Abstract

Desmoid fibromatosis is a locally aggressive neoplasm with high recurrence rate after surgery. We evaluated the use of sorafenib (400 mg/day, median duration of therapy 12 months) in four patients (median age 17 years) with recurrent or unresectable disease. All patients had clinical evidence of response and have no evidence of disease progression 2 to 13 months from discontinuation of therapy. Sorafenib is an active agent in desmoid fibromatosis and its use should be considered in the first line treatment in cases of unresectable disease.

Introduction

Desmoid fibromatosis, also known as desmoid tumor or aggressive fibromatosis, is a rare neoplasm with a tendon-like consistency that is believed to arise from fibroblasts through a mutation that activates the β-catenin pathway1. Desmoid fibromatosis accounts for approximately 0.03% of all neoplasms and <3% of soft tissue sarcomas2, most often affecting individuals between the ages of 15 to 60 years. Given the ubiquitous distribution of fibroblasts, this neoplasm can occur anywhere in the body. Although it has no known potential for metastasis, it has a locally aggressive behavior and a high recurrence rate, even after a complete resection. In fact, desmoids fibromatosis can be fatal in its ability to invade into vital structures, which is more common when it occurs in association with familial adenomatous polyposis and Gardner syndrome3. Prognosis varies based on stage, age, gender, disease extent, and location4.

Historically, management of these neoplasms has varied based on physician preference and expected course of the disease. If it remains indolent, the tumor may sometimes regress on its own5. The majority of patients are symptomatic or have progressive disease; in those
situations, upfront surgery is usually the recommended treatment when the disease is considered to be resectable. However, a large proportion of patients have unresectable lesions that progress in the absence of treatment, or have recurrent disease even after complete resection\(^{3}\). In such situations, there are no widely accepted guidelines. In patients with recurrent or unresectable disease radiation, ablation, or chemotherapy is used. Chemotherapy regimens include anthracyclines, vinca alkaloid-methotrexate combinations, single agent dacarbazine or temozolomide, or combinations of these. Overall, response rates of 20-30% have been reported\(^{6}\). Additionally, there are some case reports on NSAIDs and anti hormone therapy, particularly antiestrogens, being used with little success\(^{6}\).

Recently, Gounder et al. reported responses to sorafenib in a series of 26 adult patients with unresectable or progressive desmoids tumor\(^{7}\). Sorafenib is a tyrosine kinase inhibitor with known antiangiogenic properties that was initially approved for the treatment of advanced renal cell carcinoma, hepatocellular carcinoma, and thyroid carcinoma\(^{5}\). It inhibits both intracellular and cell surface kinases, and also works by inhibiting tumor growth and angiogenesis. It is better tolerated than most cytotoxic chemotherapeutic agents; dose-limiting toxicity includes cardiovascular toxicity, gastrointestinal perforation, hemorrhage requiring medical intervention, and dermatologic toxicity\(^{5}\). The recommended dose in the treatment of malignant conditions in adults is 400 mg every 12 hours.

**Methods:**

Following institutional IRB approval, we identified all pediatric patients with desmoid tumors who were treated with sorafenib in our institution. The medical records of the four patients identified were reviewed to collect the pertinent data on patient and tumor characteristics, prior treatments received, clinical course, treatment, toxicity, and response to sorafenib. Given the small sample size, descriptive statistics were used to determine the efficacy of sorafenib.

**Results:**

Patient characteristics are summarized in Table 1. The median age at diagnosis of desmoid fibromatosis was 11.5 years (range 9 – 17 years). Three patients had recurrent disease after different combinations of surgery, local ablation, and chemotherapy, and one patient with unresectable disease was treated with sorafenib immediately at diagnosis.

Median age at the time of treatment with sorafenib was 17 years (range 9-23). All patients had pain and functional impairment at the time of initiation of sorafenib. Sorafenib was started at 200 mg daily and was increased to 400 mg daily after approximately four to six weeks, as tolerated. Clinical improvement was typically seen in all patients within 1 to 2 months of starting therapy. Median duration of therapy was 12 months (range 9 to 12). In three patients, the treatment was electively discontinued at 12 months of initiation after documenting a maintained clinical and radiological response. One patient was 9 months into therapy at the time of writing this report. Toxicities on treatment included grade 2 fatigue (2 patients), grade 2 nausea (1 patient), grade 1 skin rash (2 patients), grade 1 hypertension (1 patient), grade 1...
weight loss (1 patient), and grade 1 neuropathy (2 patients). None of those toxic events required dose modification, interruption, or discontinuation.

All patients had clinical response, with decreased pain and improved function. Responses occurred typically after eight to ten weeks of therapy. Three patients electively discontinued treatment after 12 months, and have remained with no evidence of disease progression 1 to 12 months since stopping therapy (median 8 months). Patient 2 is still receiving therapy.

Discussion:

Herein we have shown evidence of significant clinical response to sorafenib in four adolescent patients with desmoid fibromatosis; treatment was overall very well tolerated at low to intermediate doses, as reported by Gounder et al. in a series of adult patients.

Desmoid fibromatosis varies significantly among patients, both in its clinical presentation as well as in its natural course, thus providing a treatment challenge. Although desmoid tumors do not metastasize, they can be locally aggressive, often infiltrating into vital organs leading to significant morbidity. There are no uniformly accepted guidelines for the first line treatment of desmoid tumors. In this cohort, all patients showed evidence of response; three of the four patients finished a 1-year course of therapy with sorafenib, with good clinical response and have not shown signs of progression at a median of 8 months since stopping treatment. Although the fourth patient is still too early in his treatment plan to see definite change, clinical response appears promising. The consistent pattern of clinical responses in all cases suggests that sorafenib is an active agent in the management of desmoids fibromatosis and it should be considered among first therapeutic options in patients with unresectable of recurrent disease. There remains the possibility of spontaneous regressions, although three out of the four patients had tried numerous treatments prior to sorafenib.

Limitations of this study include its retrospective nature, the small sample size, the relatively short follow-up, and lack of radiographic correlation. A prospective, randomized clinical trial of sorafenib against other agents with a larger patient population is warranted.
Table 1:

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>Age at diagnosis</th>
<th>Site</th>
<th>Prior treatments</th>
<th>Age at treatment</th>
<th>Dose (duration)</th>
<th>Clinical Response</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>16</td>
<td>Foot</td>
<td>None</td>
<td>16</td>
<td>400 mg (12 months)</td>
<td>Decreased pain</td>
<td>Full function recovery</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>16</td>
<td>Leg</td>
<td>Surgery Cryotherapy M, V, D, H</td>
<td>23</td>
<td>400 mg (ongoing)</td>
<td>Decreased pain</td>
<td>Ongoing therapy</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>17</td>
<td>Leg</td>
<td>H</td>
<td>19</td>
<td>400 mg (12 months)</td>
<td>Decreased pain</td>
<td>Full function recovery</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>9</td>
<td>Arm</td>
<td>Surgery Cryotherapy Chemical ablation M, V</td>
<td>15</td>
<td>400 mg (12 months)</td>
<td>Decreased pain</td>
<td>Full function recovery</td>
</tr>
</tbody>
</table>

Abbreviations: M, male; F, female; M, methotrexate; V, vinblastine; D, liposomal doxorubicin; H, hydroxyurea


