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CORR Insights®: PROMIS Function Scores Are Lower in Patients Who Underwent More Aggressive Local Treatment for Desmoid Tumors

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Where Are We Now?

During the last several decades, treatment for desmoid tumors has evolved away from surgery and toward fewer and less-invasive operations. I believe this movement started when a study on Gardner's syndrome (familial adenomatous polyposis) found that sulindac and indomethacin plus high-dose vitamin C caused regression of intestinal polyps, resulting in fewer colorectal cancers, as well as a decrease in desmoid tumors [10]. While selective estrogen-receptor inhibitors or of low-dose chemotherapy (methotrexate and vinblastine) are seeing wider use [11], the pendulum swung further away from surgery when a study found that negative margins did not predict remaining recurrence free, nor were positive margins routinely associated with local recurrence [2].

More-sophisticated, targeted therapies have achieved high response rates [4]. One study found an 87% lower risk of progression or death in a group treated with sorafenib than in the placebo group, although 12% still progressed while on the active drug [4]. Responses can be monitored by assessing the relative cellularity of the tumor, since it is the cellular component that can grow and shrink far more dramatically than the relatively stable fibrous component [4]. This approach has become the first-line treatment for desmoid tumors. However, the responses to targeted agents are time-dependent, and can take many months; as a result, patients often are treated for 1 to 2 years. Despite prolonged therapy, patients had partial response rates of 33% by RESIST 1.1 criteria. The favorable news is that disease rarely progressed while on these targeted therapies. However, the toxicity of treatment can be severe. Palmar-plantar erythrodysesthesia (painful redness, swelling and sometimes blistering, often referred to as hand-foot syndrome) occurs in about 20% of patients and hypertension in 9.4% to 18.9% of patients [8].

In the current study, Newman and colleagues [7] use the Patient-Reported Outcomes Measurement Information System (PROMIS) to assess the quality of life (QOL) of patients treated for desmoid tumors. Because desmoid tumors are a local disease, where the treatment can be worse than the disease, QOL and patient satisfaction are very important outcomes to consider.

Where Do We Need to Go?

In the current study, none of the QOL measures addressed the tumor treatments' most-frequent and severe side effects, such as fatigue, hypertension, diarrhea, and hematopoietic toxicity [7]. Since desmoid tumor is predominantly a condition of young women of potential child bearing age, this is something that should be assessed in future studies.

Disease and treatment-related morbidity are not confined to the musculoskeletal system, as suggested by use of PROMIS and conventional orthopaedic oncologic systems. Men should also be cautioned to avoid fathering a child for up to 3 months after

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completing therapy with sorafenib, due to alterations in sperm count, shape, and motility that alter teratogenicity and fertility in preclinical models [8]. These wider concerns should cause us to ask important questions, like whether a patient would choose a painful scar and limp over hypertension and the risk of fetal deformity? The surgeon and oncologist need to guide the young person deftly through a tough decision-making process for which there is no perfect answer.

Although treatments for desmoid tumors have proliferated, there has been little high-quality research to define the preferred approach. Indeed, the presence of so many treatments suggests that none is clearly superior. There also is no consensus regarding how to balance local tumor control, risk of recurrence, or the morbidity of aggressive surgical treatment.

Disease recurrence is a binary outcome, but QOL measures are multi-parameter continuous variables. How do we determine which is more important and when do we make such an assessment? Furthermore, both local recurrence and QOL have different consequences based on tumor location. The current study raises important concerns, but it can't resolve questions about the most appropriate therapy for the individual patient. This uncontrolled, retrospective, observational report is hypothesis-generating and doesn't convincingly answer the questions posed. Furthermore, the differences between patients and tumors preclude collecting a sufficiently homogeneous population to make even a randomized trial meaningful.

Therefore, we should consider more fundamental aspects of the disease and treatment, stipulating that methodologic limitations prevent us from reconciling disproportionate outcomes, such as recurrence and QOL. We need to define a way forward that will build on the current study's results and establish a foundation upon which to analyze and treat desmoid tumors [7].

We need to better understand the cause of this disease. "Medical treatments", as advocated in this study, are non-specific. Targeted therapy is the thrust of modern oncologic therapy. Basic science investigation is to understand the mesenchymal stem-like cell that starts the disease is a beginning [12]. Metabolomics and high throughput screens have been aggressively investigated recently with encouraging results regarding our ability to create more specific and safer treatments [1, 6].

How Do We Get There?

Solving the problem of this disease will be complicated and will require a number of parallel approaches. Basic research needs to be done under the auspices of government, drug companies, and private enterprise. This will identify more-effective targeted drugs for this indication. Professional organizations, such as The Musculoskeletal Tumor Society (MSTS), should sponsor this work. In conjunction with organizations such as the Orthopaedic Research and Education Foundation, appropriate small clinical trials could then be sponsored, comparing new treatments versus standard therapies. With the enthusiastic sponsorship of the MSTS, our members would have the incentive to enroll patients in a suitable clinical trial, a problem that impedes progress in the treatment of all rare diseases [4]. Assuming that a new trial would test a drug, it would require collaboration with our medical oncology colleagues, and perhaps the Connective Tissue Oncology Society. PROMIS or the Toronto Extremity Salvage Score should be selected as the accepted outcome assessment tool and the standard for publication in this field. New, disease-specific outcome measures are under development with the sponsorship of the American Society of Clinical Oncology. They will hopefully address the shortcomings of the current systems and could also be used [9]. When we have truly targeted, disease-specific therapies available, then the toxicities may be worth accepting. Until then, surgery remains an option to remove the most accessible of these tumors.

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