FEASIBILITY OF PRE-OPERATIVE mTOR INHIBITOR SIROLIMUS IN CHILDREN AND YOUNG ADULTS WITH DESMOID TUMOR

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Objective:

Desmoid tumor (DT) represents an intermediate grade neoplasm with a striking predilection for locally invasive growth and recurrence following resection. More effective, well-tolerated non-surgical treatment options are needed. DT is well-known to be associated with deregulation of the APC/β-catenin pathway. Deregulation of the mTOR cell proliferation/survival pathway may play an important role in tumor biology when the APC/β-catenin pathway is disrupted. Sirolimus, an mTOR inhibitor, is attractive as a potential targeted therapy for DT because it is well-tolerated in children and young adults and it can be given orally. A pilot study was designed to determine whether sirolimus can block the mTOR pathway (primary aim), safely be given in the pre-operative setting, decrease tumor size/recurrence, and decrease tumor-associated pain in children and young adults (secondary aims) with DT.

Methods:

This multi-institutional study is open and actively accruing for patients < 30 years of age who have surgery planned to remove their DT and either (a) it has already recurred after a prior surgery or (b) the newly diagnosed and/or previously unresected disease is judged to be at high risk for recurrence due to its size (> 5 cm) or location at an anatomic site making it unlikely to be resected with negative margins (e.g., adjacent to neurovascular structures). Patients receive 4 weeks of pre-operative sirolimus. Surgical resection should be accomplished within 3 days of completing therapy. To assess mTOR pathway activation, immunohistochemical (IHC) staining will be conducted for p70S6KThr³⁸⁹, p4E-BP1Ser⁶⁵, and pAKTThr³⁰⁸ on the (a) post-treatment specimens, (b) paired, pre-treatment, archived specimens (if available), and (c) archived non-chemotherapy-treated specimens. Validated pain assessment measures and anatomical imaging are being performed at designated surveillance intervals. This is an IRB-approved study and patient consent is required.

Results:
Nine of an anticipated 15 total patients have enrolled to date. Ages have ranged from 5 to 28 years. All patients have been able to take the pre-operative sirolimus as prescribed and undergone surgery within the protocol-directed time frame. All toxicities have been as expected and Common Terminology Criteria for Adverse Events grade 1 and 2 only except for one grade 3 neutropenia. No post-operative complications have been reported. IHC staining is ongoing for p4E-BP1, p70S6K, and pAKT (Figure 1).

Conclusion:

Sirolimus appears to be well-tolerated when administered in the pre-operative setting to children and young adults with DT. Surgery is feasible and safe immediately after completing therapy. Formal assessment of the mTOR pathway by IHC analysis will take place at study completion. The study continues to actively accrue.
Figure 1: Representative pre- and post-operative IHC staining for mTOR pathway proteins p4E-BP1 (A), p70S6K (B) and pAKT (C) in desmoid tumor.