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Feasibility of pre-operative mTOR inhibitor Sirolimus in children and young adults with desmoid tumor

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Background
• Desmoid tumor 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
• Current approaches
  • If feasible, watchful waiting is the preferred approach
  • 20-30% spontaneous regression
  • In situations where treatment is indicated, the following approaches are utilized
    • Surgery is the primary approach if minimal morbidity is anticipated
    • Medical therapies
      • Cytotoxic drugs
      • Tyrosine kinase inhibitors
      • Hydroxyurea
      • Gamma secretase inhibitors
• mTOR Inhibitor Rationale
  • Desmoid tumor 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
  • The mTOR inhibitor sirolimus is attractive as a potential targeted therapy for desmoid tumor
  • Well-tolerated in children and young adults
  • Can be given orally in tablet or liquid formulation

Objectives
• Primary
  1. To determine whether mTOR pathway activation decreases in patients with surgically resectable desmoid tumor that is removed following pre-operative treatment with sirolimus
• Secondary
  1. To assess whether sirolimus improves desmoid tumor-associated pain
  2. To begin to explore whether pre-operative sirolimus decreases tumor recurrence following surgical removal of desmoid tumor felt to be at high-risk for recurrence because of size and/or anatomic site
  3. To assess the safety and tolerability of pre-operative sirolimus in patients with desmoid tumor

Methods
• Multi-institutional study open and actively accruing patients
• Eligibility criteria
  • <30 years of age
  • Surgery is planned to remove their desmoid tumor and either
    • (a) the desmoid tumor has already recurred after a prior surgery or
    • (b) the newly diagnosed 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 with germline APC causing FAP/Gardner’s syndrome
  • 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 2)
• Pain assessment measurements and anatomical imaging are being performed at designated surveillance intervals

Histologic Assessment
• Tissue
• Pre-therapy biopsy
• Post-therapy biopsy
• Archived specimens (future analysis)
• Paired, pre-treatment
• Non-chemotherapy treatment

Figure 2. Representative pre- and post-operative IHC staining for mTOR pathway proteins p4E-BP1, p70S6K, and pAKT in desmoid tumor

Conclusion
• Sirolimus appears to be well-tolerated when administered in the pre-operative setting to children and young adults with desmoid tumor
• 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

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