Combination Chemotherapy for Aggressive Fibromatosis: Preliminary Results From Beta-Catenin inhibitor, Dexamethasone, and Focal Adhesion Kinase Inhibitor

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Introduction

- Aggressive Fibromatosis (AF) is a benign but locally aggressive lesion.
  - Surgical resection is associated with high local recurrence rates.
- Multiple studies have explored chemotherapeutic options for AF.
  - Few studies have employed combination therapy.
- A large drug screen at the investigating institution revealed numerous FDA approved medications with promising activity in AF.
- We sought to investigate the utility of combination therapy for FDA approved medications to expedite patient care through translational research

Methods

- *Apc*$^{+}$*/Apc*^{1638N} mice, which develop AF lesions (shown previously), were treated with:
  - BC2059 – a beta catenin inhibitor
  - Focal Adhesion Kinase (FAK) inhibitor
  - Dexamethasone (Dex)
    - These drugs were selected due to their activity in AF in prior drug screen
- Mice were sacrificed at 6 months following chemotherapy treatment
  - Tumor size and number determined by blinded members of the research team
- Cellular markers of proliferation and apoptosis were analyzed through IHC
  - Real time PCR, western blot, downstream beta catenin activity, and human cell cultures pending analysis

Statistical Analysis

- IHC markers analyzed with ImageJ and ANOVA was used for comparison of average tumor number, size, and cellular activity between treatment groups

Results

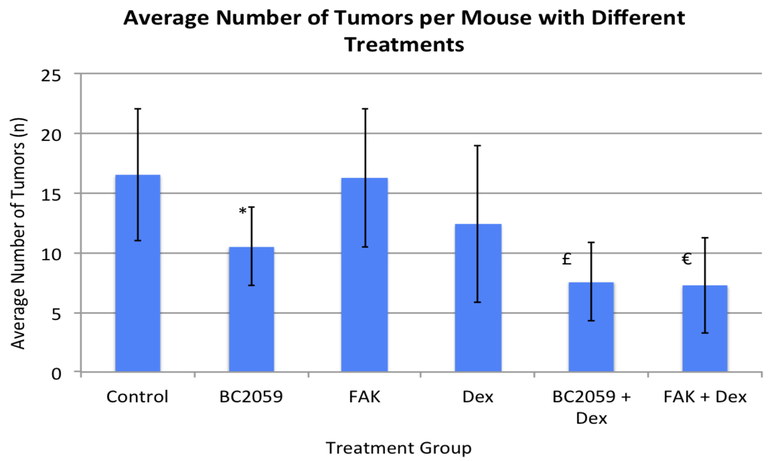


Figure 1: Comparison of average number of tumors per mouse in different treatment groups. Data is presented as average with standard deviation error bars. Compared to the control group, BC2059 (*-p=0.0004), BC2059 with Dexamethasone (£-p<0.0001), and FAK inhibitor with Dexamethasone (€-p<0.0001) showed significant decrease in total number of tumors.

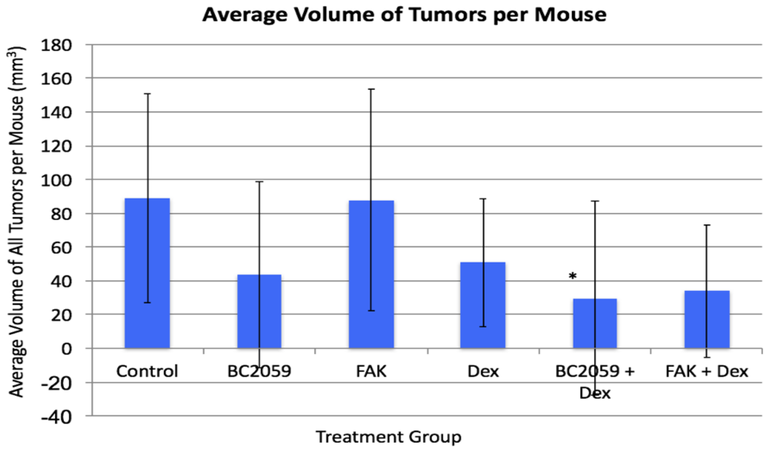
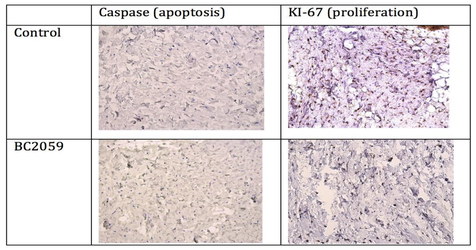


Figure 2: Comparison of average volume of all tumors per mouse in different treatment groups. Data is presented as averages with standard deviation error bars. Compared to the control group, only BC2059 with Dexamethasone (*-p=0.047) showed significant decrease in tumor size, while other groups trended towards decreased tumor size.

- Representative histology and IHC for KI67 and Caspase



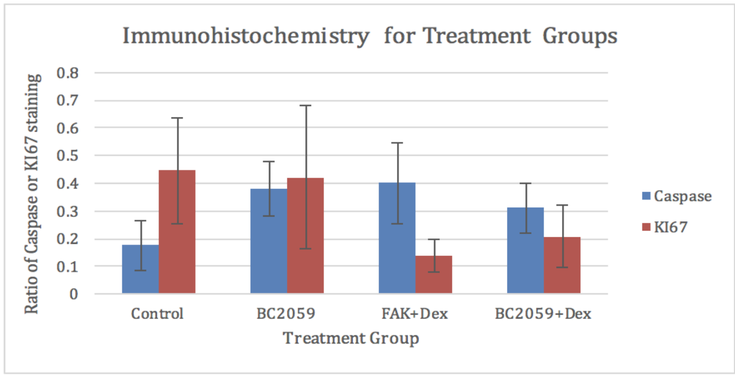


Figure 3: Ratio of Caspase or KI67 staining for different treatment groups. Data is presented as average with standard deviation error bars. There was no significant difference in Caspase or KI67 activity between groups. Combination therapy with FAK+Dex trended toward the greatest decrease in proliferation and increase in apoptosis.

Conclusions

- Combination therapy for Aggressive Fibromatosis can suppress proliferation and increase apoptosis, thereby significantly decreasing tumor number and volume in murine models.
- FDA approved medications discovered through a prior drug screen requires further investigation for potential utility in the clinical setting in combination clinical trials

Acknowledgements

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