DANA-FARBER CANCER INSTITUTE

CENTER FOR SARCOMA AND BONE ONCOLOGY

LEIOMYOSARCOMA

RESEARCH DESCRIPTION

Defining the genomic landscape

Leiomyosarcoma can arise almost anywhere in the body and varies dramatically in its progression. Despite this heterogeneity, for many years it was thought that leiomyosarcomas had the same genomic underpinnings. New indicators show this may not be true.

Suzanne George, MD, clinical director of the Center for Sarcoma and Bone Oncology, collaborated with investigators at the Broad Institute of MIT and Harvard to undertake an unprecedented genomic analysis of leiomyosarcoma. The aim is to explore the possibility of different mutations that fuel the growth of leiomyosarcoma. Deconstructing the heterogeneity of leiomyosarcoma could improve patient outcomes by affording researchers the opportunity to develop targeted therapeutics based on the differences in disease presentation.

Dr. George and her colleagues began by identifying some of the most obvious differences among leiomyosarcomas – location and histology. Histology is a critical tool for the examination of tissue samples, allowing scientists to study the microscopic anatomy of tissue and differentiate healthy tissue from diseased tissue.

As part of their investigation, Dr. George and her colleagues will study samples from each of the three histological groups (non-uterine, myxoid uterine, and high-grade spindle cell uterine), and each group will consist of samples from 10-20 consenting patients who received at least part of their care at Dana-Farber. Healthy blood cells from each participant will be analyzed to create the "background" sequence that allows acquired cancer-driving mutations to be identified by comparison. In addition, because cancer cells evolve as tumors spread, samples from metastatic sites will be sequenced to isolate the mutations that drive metastasis. Once all of the samples are collected, investigators at the Broad Institute will analyze the DNA and RNA.

A critical part of this study is correlating the genomic findings to the clinical data, which includes disease progression and treatment response. Dr. George envisions that, with the help of biostatisticians, the data may reveal genetic hallmarks that confer specific clinical traits of the disease, such as tumor spread or resistance. Even in the absence of these correlations, the study will bridge a critical gap in knowledge about the genomic landscape of leiomyosarcomas.

Deconstructing heterogeneity in leiomyosarcoma

The majority of leiomyosarcomas stabilize upon treatment with pazopanib; smaller subsets significantly regress. Dr. George aims to identify the dramatic responders and study what genetic characteristics differentiate them from others. The study will use archived tumor samples in order to accelerate the

investigation. Dr. George intends to retrospectively analyze treatment response to pazopanib based on patient records and run genomic analysis on corresponding samples. This will ultimately enable more tailored treatment based on a tumor's genetic profile.

In a separate study, Dr. George found that the drug letrozole has a small anti-cancer effect in patients with hormone-dependent uterine leiomyosarcomas. In 2012, Dr. George presented these results at the Connective Tissue Oncology Society conference in Prague. Knowing that letrozole is effective for treating specific types of uterine leiomyosarcoma – but may not work against other types of sarcoma – helps physicians to identify those patients who are most likely to respond to the drug. Dr. George is considering a combination trial with an mTOR inhibitor that may result in improved response to letrozole in certain patients. Because opening such a trial requires proof of concept, a literature review is underway to identify reports of existing research models of uterine leiomyosarcoma that are highly dependent on estrogen signaling.