

Dana-Farber to present research on myeloma progression from precursor conditions

December 4 2018

Dana-Farber Cancer Institute scientists will present research marking significant advances against the hematologic cancer multiple myeloma at the American Society of Hematology (ASH) Annual Meeting Dec. 1-4. Their findings provide new insights into the progression of the disease from precursor conditions and suggest approaches for novel treatments.

In related work, Dana-Farber investigators will also present a novel system for classifying [patients](#) with smoldering Waldenström macroglobulinemia by their likelihood of developing Waldenström's itself.

Here are some examples of this research:

Immune response may predict risk of progression to myeloma in patients with precursor conditions, study finds

Even before people with premalignant stages of multiple [myeloma](#) develop symptoms, immune system cells in their bone marrow undergo a variety of changes that affect the progression to myeloma, Dana-Farber scientists report in a new study. The findings, which offer the first detailed look at the interplay between malignant and immune cells in patients with myeloma precursor conditions, may lead to tests for predicting the advance of the disease and, potentially, to new strategies for treating it.

The study involved analyzing gene activity in individual plasma cells and immune system cells from the bone marrow of healthy people and patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma, which are precursor conditions of myeloma. The analysis was performed by sequencing the RNA in each cell, providing an indication of which genes are active.

Researchers found that even at the earliest, premalignant stages of the disease, the immune microenvironment—the collection of immune cells in the bone marrow—undergoes a dramatic shift from that of healthy people. They found, for example, an influx of [immune system cells](#) called natural killer cells, macrophages, and T cells in patients with precursor conditions, as well as changes in surface molecules on plasma cells that made the cells harder for the immune system to detect.

"For the first time, we identify changes in immune cells that are present in the bone marrow microenvironment of patients at early stages of the disease, even at the MGUS stage," said Irene Ghobrial, MD, the principal investigator of the trial and co-director of the Center for Prevention of Progression of Blood Cancers at Dana-Farber. "We also define specific changes in these [immune cells](#) that can be targeted in the future with immunotherapy to prevent or intercept disease progression, making myeloma potentially a preventable disease."

Researchers will present their findings at [Session 602](#), on Sunday, Dec. 2 at 6:00 p.m. PST in Hall GH of the San Diego Convention Center.

Three-drug combination produces broad response in patients with high-risk smoldering multiple myeloma

In the vast majority of patients with high-risk smoldering multiple myeloma (SMM), a combination of the drugs ixazomib, lenalidomide,

and dexamethasone can substantially reduce the extent of their cancer with minimal side effects, initial results from a phase 2 clinical trial led by Dana-Farber researchers suggest.

The interim findings of the trial, which involved 29 patients with high-risk SMM, will be presented at [Session 653](#), on Monday, Dec. 3, at 4:00 p.m. in Room 6F of the San Diego Convention Center. Among the participants who received at least three cycles of the three-drug regimen, 89 percent responded to the treatment, meaning they had at least a 30 percent reduction of their disease. Five of those patients had a complete response—a disappearance of all signs of cancer—and nine had a response characterized as very good. None of the participants, who began therapy between February 2017 and April 2018, have developed symptoms of myeloma.

The combination had minimal toxicities. The common side effects of the therapy were mild to moderate fatigue and rash. Severe (grade 3) hypophosphatemia (low phosphate levels in the blood) occurred in two patients, while grade 3 neutropenia (a reduction in the number of white blood cells) was found in only one patient.

Ixazomib is a proteasome inhibitor, which interferes with a structure in cells that breaks down unneeded proteins; lenalidomide kills cancer cells by a variety of mechanisms; and dexamethasone is a corticosteroid.

"Early intervention in patients with high-risk SMM has been shown to be a better approach to delaying or preventing progression of this cancer," said Dana-Farber's Mark Bustoros, MD, who is presenting the results of the trial at the ASH annual meeting. "We are expanding on that approach with this convenient drug combination. Patients with high-risk SMM have a higher chance of progression within a short period of time, yet they are asymptomatic and have their regular personal and professional lives. Providing this oral combination brings advantages of both efficacy

and convenience."

"This is the first time we have seen a high response rate, including over 50 percent complete remission and very good response rates, in patients with high-risk smoldering myeloma using a well-tolerated combination of oral therapies," said Ghobrial. "We believe this could be a platform for therapy in the near future for patients with smoldering myeloma who are at high risk of disease progression and who benefit from early intervention."

Study identifies ID2-related pathways as potential drug targets in multiple myeloma

The search for potential drug targets in multiple myeloma has turned up a promising new candidate. In a study led by Dana-Farber scientists, researchers report that a protein called inhibitor of DNA binding 2 (ID2) helps suppress tumor cell growth and is significantly downregulated, or under-produced, in myeloma cells. By blocking proteins that keep ID2 production abnormally low, new targeted therapies could potentially restore the brakes on tumor cell proliferation.

By comparing the expression of ID2 (and the three other members of the ID protein family) in normal plasma cells and myeloma cells from 360 patients with the disease, researchers found that ID2 was sharply downregulated in the myeloma cells. When they overexpressed ID2 in myeloma cell lines, the cell proliferation rate dropped markedly.

Investigators next explored the mechanism that causes ID2 to be downregulated. In a series of experiments, they found that [bone marrow](#) stromal cells—which give rise to a variety of skeletal components such as bone and cartilage, supportive tissue, and fat cells—can interact with myeloma cells to reduce ID2 production.

"This study identifies a new mechanism in which genes act as decoy to increase function of other target genes," said the study's lead author, Nikhil Munshi, MD, director of Basic and Correlative Science at the Jerome Lipper Multiple Myeloma Center at Dana-Farber. "It provides clues to some of the less understood molecular mechanisms in myeloma and may lead to new therapeutic interventions." The lead author of the study is Tommaso Perini, MD, of the LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center at Dana-Farber, and University Vita-Salute San Raffaele, in Milano, Italy.

Researchers will give an oral presentation of their findings at [Session 651](#), on Saturday, Dec. 1, at 8:45 a.m. in Grand Ballroom 7 of the Marriott Marquis Sand Diego Marina.

Researchers launch screening study of individuals at high risk of multiple myeloma

Researchers at Dana-Farber are seeking participants in a new study, funded as part of the [Stand Up To Cancer Multiple Myeloma Dream Team](#), to identify people with conditions that are precursors of multiple myeloma and track their health over time. The study, dubbed PROMISE, will help scientists track the molecular changes that occur as precursor conditions—monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma—progress to myeloma. This information will be critical in the development of drugs that prevent the disease from advancing and improve patients' survival.

The study is open to two groups of individuals between the ages of 45 and 75 who have been identified to be at high risk of multiple myeloma and its precursor conditions:

- African Americans, who are three times more likely than

Caucasians to develop MGUS;

- People with a first-degree relative (a parent, sibling, or child) with a plasma cell disorder such as multiple myeloma.

Participants will complete an online health questionnaire, provide [blood samples](#) periodically for analysis, and submit updated health information periodically. Participants whose blood samples test positive for a myeloma precursor condition will be assisted in scheduling an appointment with a hematologist/oncologist. They will also be asked to submit health information and blood samples every 3-6 months and may be eligible for clinical trials exploring treatments to prevent progression. These samples will be analyzed for molecular signs indicating the risk of disease progression.

"Our hope is that by screening and identifying the precursor conditions early, we can understand the molecular signs of progression to myeloma, and develop therapies that will replace 'watch and wait' and make myeloma a preventable disease," said Ghobrial, the study's principal investigator.

Initial participation in the trial is online or by mail. Local travel for blood draw is required. Testing will be performed at each participant's local Quest Diagnostics laboratory. To sign up for the study, please visit <http://www.promisestudy.org>.

Researchers devise risk-based classification system for patients with smoldering Waldenström macroglobulinemia

By analyzing data from hundreds of patients with smoldering Waldenström macroglobulinemia (SWM), researchers at Dana-Farber have devised a [risk model](#) for determining whether patients with SWM

have a low, intermediate, or high risk of developing Waldenström's macroglobulinemia (WM).

Under this system, patients' risk is assessed using four measures: Bone marrow lymphoplasmacytic infiltration; serum immunoglobulin M levels; β 2 microglobulin levels, and albumin levels. Stratifying patients into three risk groups based on these variables can improve patient monitoring and, importantly, identify high-risk patients who might benefit from early intervention, researchers say.

Waldenström macroglobulinemia is a low-grade form of non-Hodgkin lymphoplasmacytic lymphoma associated with overproduction of monoclonal IgM protein and is often preceded by SWM, an asymptomatic condition. "Patients with WM usually have symptoms of anemia, peripheral neuropathy, bleeding and other problems," said Bustoros, the study lead, who is presenting the final results at the ASH annual meeting. "Almost two-thirds of patients with SWM progress to the symptomatic stage. Higher values of the four biomarkers were associated with a significant risk of progression to symptomatic disease within few years. We will provide this model as an open access web application so it can help oncologists improve the care and guide the management of patients with this rare cancer."

"The model was generated based on 439 patients with SWM at Dana-Farber and was validated using two other cohorts, from the Mayo Clinic and University of Athens in Greece," said Dana-Farber's Romanos Sklavenitis Pistofidis, MD, first co-author of the study. "The model was a strong predictor in identifying high-risk patients, intermediate, and low-risk ones with high accuracy and precision."

"We hope this model will help in identifying patients at high risk of disease progression so they can be followed up closely or benefit from early treatment approaches through clinical trials," said Ghobrial, the

senior author of this study.

Provided by Dana-Farber Cancer Institute

Citation: Dana-Farber to present research on myeloma progression from precursor conditions (2018, December 4) retrieved 8 May 2024 from <https://medicalxpress.com/news/2018-12-dana-farber-myeloma-precursor-conditions.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.