CASSINI Trial publishes data on preventing blood clots in cancer patients

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The first clinical study investigating the use of the direct oral anticoagulant, rivaroxaban, to prevent blood clots in patients with cancer at high-risk published today in the *New England Journal of Medicine*. The study found no significant reduction in venous thromboembolism or death in the overall 180-day trial period; however, the researchers did observe a lower incidence of these events while patients were actively on the study drug, or during the on-treatment period.

Known as the CASSINI Trial, the study was led by senior author Dr. Gary H. Lyman, senior lead for health care quality and policy at Fred Hutchinson Cancer Research Center and first author and primary study lead, Dr. Alok Khorana, Director of Gastrointestinal Malignancies at the Cleveland Clinic and included co-senior author, Dr. Nicole M. Kuderer, who performed this research in part at the Advanced Cancer Research Group and at the University of Washington. The CASSINI Trial was a multicenter, randomized Phase IIIb trial that enrolled 1,080 patients from the U.S. and internationally.

Cancer patients have an increased risk of blood clots, which are elevated by biologic factors of cancer that can alter and thicken the blood and by many types of cancer treatments, including chemotherapy.

"After the cancer itself, blood clots are the second leading cause of death, along with infection, in real-world cancer outpatients receiving chemotherapy, and a major cause of morbidity, mortality and increased costs among patients hospitalized with a blood clot," said Lyman. "The

results of this study will help us understand how we should weigh the potential benefits of reducing blood clots with potential risks, and how to establish a standard for assessing which cancer patients are at the highest risk of developing blood clots."

While a significant reduction in risk of venous thromboembolism was observed during the on-treatment period, the study did not find a significant impact on its primary outcome of venous thromboembolism during the first 180 days, during which time many patients came off the study drug to a similar extent in both the intervention and placebo arms. Overall, there was a low risk for major bleeding during both the 180-day trial and on-treatment periods.

Along with a second oral anticoagulant study, the AVERT Trial, the CASSINI Trial presents the first large-scale data on the safety and efficacy of new oral anticoagulants as preventive agents for blood clots in cancer patients. The CASSINI and AVERT Trials also represent the first Phase III studies utilizing a validated clinical risk score, The Khorana Risk Score, to identify ambulatory cancer patients at increased risk for venous thromboembolism.

"While screening patients for blood clots prior to entering this study, we identified nearly five percent with a Khorana Risk Score of two or greater who already had unrecognized blood clots despite physical exam prior to starting chemotherapy," commented Kuderer. "This confirmed our previous study where screening identified blood clots in nearly nine percent of higher-risk patients who had a Khorana Risk Score greater than or equal to three. These blood clots would otherwise have remained untreated for some time, potentially only being recognized once they traveled to the lungs, at which point some of these clots can be deadly."

The risk of blood clots after a cancer diagnosis increases over the entire period of active cancer and cancer treatment, ranging on average from

five to 25 percent across different cancer types, particularly in patients with advanced disease. Blood clots can lead to serious complications like pulmonary embolism.

"Larger studies in real-world patients will be needed to determine whether screening, as in the CASSINI Trial, can reduce early mortality in this setting," said Kuderer.

In order to assess which patients were at high-risk for developing blood clots, the researchers used the Khorana Risk Score based on cancer type, body-mass index and blood counts. The CASSINI Trial screened all patients prior to randomization, identifying by ultrasound those who already had blood clots. One key distinction between these two studies is that the CASSINI Trial screened participants for blood clots prior to as well as during the study period, while the AVERT Trial did not.

"While the CASSINI and AVERT Trials differ with regard to screening and certain outcome measures, I consider these studies to be complementary and encourage that they be interpreted together, taking into account the design differences," said Lyman. "I am also hopeful that future trials will further improve our ability to risk stratify patients perhaps by including the type of treatment and validated biomarkers."

Direct oral anticoagulants are not presently approved for use in preventing blood clots in cancer patients. The current standard of care recommends a drug which must be injected to treat blood clots after they develop or as a preventive agent in selected, high-risk patients. As cancer therapy is frequently delivered in outpatient settings, the CASSINI Trial sought to evaluate whether a risk-stratified approach and use of an oral anticoagulant could present a safe, effective and more convenient option for preventing blood clots in patients with cancer.

As a next step, Lyman and colleagues at Fred Hutch are hoping to

embark on a cost utility analysis which incorporates impact on patients' quality of life with drug and other health care costs. In addition, they are collaborating on a meta-analysis of the CASSINI and AVERT Trials to present a more complete understanding of the use of the oral anticoagulants as preventive agents.

"There's a longstanding need for the oncology and hematology communities to address this issue holistically and understand the true burden blood clots and related conditions and hospitalizations have on cancer patients," said Lyman. "The results of these important trials will be intensely studied by the guideline panels to assess whether changes in current guideline recommendations are warranted."

Lyman is co-leading guideline efforts for treating or preventing blood clots in patients with cancer for the American Society of Clinical Oncology, as well as the American Society of Hematology, which is establishing treatment guidelines for blood clots in several clinical settings.

"In my early days as an oncologist in Buffalo, New York, I first observed the devastating impact blood clots had on many patients," commented Lyman. "Since then, we have pursued numerous research leads to advance our understanding of how we can best prevent serious adverse outcomes caused by blood clots."

More information: *New England Journal of Medicine* (2019). DOI: 10.1056/NEJMoa1814630

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