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Clinical trials of new cancer drugs may inappropriately exclude people of African/Middle Eastern descent

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Many clinical trials of new cancer drugs may be inappropriately excluding some people with "Duffy-null phenotype," a trait found

predominantly in people of African or Middle Eastern descent, researchers at Dana-Farber Cancer Institute and Queen Mary University of London report in study published in *JAMA Network Open*.

The Duffy-null phenotype results in relatively lower levels of white blood cells called neutrophils when measured in the blood. This is not because they have less neutrophils overall, but because they are more frequently located in other body tissues.

Tests that restrict clinical trial eligibility to patients with certain blood levels of neutrophils may therefore be unfairly discriminating against patients who could potentially benefit from trial therapies.

The failure to account for Duffy-null phenotype also means that recommendations for many standard cancer drugs inappropriately call for less-effective doses for some individuals, researchers say.

Tests that count neutrophils in a blood sample are performed to ensure that patients can safely be treated with chemotherapy or other anti-cancer drugs. Levels of neutrophils, white blood cells that kill bacteria and other foreign microbes, are often reduced by cancer drugs, potentially raising the risk of infection.

For patients to qualify for a clinical trial or a standard dose of many cancer drugs, their neutrophil levels need to be above a certain threshold to ensure they will retain enough of these cells following treatment.

The threshold was established by studies conducted primarily in patients of European descent who rarely have the Duffy-null phenotype. Many healthy people with the Duffy-null phenotype (mostly people of African and Middle Eastern ancestry), however, normally have lower levels of neutrophils in their blood and relatively higher levels in their other tissues.

"Natural variation in neutrophil counts between people of different ancestry has been historically described by the inaccurate and now-outdated diagnosis 'benign ethnic neutropenia,'" says Stephen Hibbs of Queen Mary University of London, who led the study for which Dana-Farber's Andrew Hantel, MD is senior author.

"But since this variation was discovered to be caused by the Duffy null phenotype, we need to re-examine the ways in which neutrophil count misinterpretation can affect patient care."

"People with the Duffy-null phenotype are equally able to fight off infections compared to others," Hantel says. "The concern is that they've been excluded from clinical trials because the neutrophil blood levels that are normal for them can fall below the cut-off points for trial participation. In this study, we explored the extent to which this occurs."

The researchers examined participation criteria for 289 major Phase III trials of drugs for the five most prevalent cancers in the United States and United Kingdom: prostate, breast, colorectal, and lung cancer, and melanoma. The drugs included chemotherapy agents, targeted therapies, and hormonal therapies (which generally don't decrease neutrophil levels).

They found that 76.5% of the trials excluded patients whose blood neutrophil counts were in the normal range for people with the Duffy-null phenotype. The trials with the highest exclusion rate—86.4%—were for patients with colorectal cancer. Even trials of hormonal cancer therapies—which generally don't decrease neutrophil levels—had a significant exclusion rate.

The researchers also examined the extent to which clinical trial protocols require that drug doses be modified for patients with lower neutrophil counts.

"The treatment guidelines set by the National Comprehensive Cancer Network, or NCCN, are based on the clinical trials in which those drugs were tested," Hantel explains.

"If a trial stipulates that the dosage should be lowered or delayed if a patient's blood neutrophil count is below a certain level, doctors often use those modifications once the drug is approved as standard therapy. We know that in many cases, survival rates are lower for patients who receive lowered or delayed doses."

The researchers reviewed 71 clinical trials that led to NCCN recommended treatment regimens. They found that more than half required reducing the drug dose, delaying its administration, or stopping it if a participant's neutrophil count fell below a level that was still normal for people with the Duffy null phenotype.

When they looked at recommended changes based on individual Food and Drug Administration labels for each therapy used, a similar rate of dose changes was seen.

"The effect of these recommendations is to inappropriately reduce the intensity of treatment for patients who would likely tolerate regular doses," Hantel says.

Based on their findings, the researchers recommend that clinical trials of cancer drugs allow entry to patients with lower, but normal-for-them neutrophil counts. "Everyone being screened for trial entry should be tested for the Duffy-null phenotype. If they are Duffy-null and their counts are in the reference range for that group, they should be admitted," Hantel remarks.

For current and future trials, the same principle should be used in determining whether trial participants require lower or delayed doses:

people with Duffy-null phenotype whose neutrophils are in their healthy range should be eligible for full doses of the study drug. For trials that have already been completed, follow-up studies are needed to determine if administering full doses to people with Duffy-null phenotype and lower neutrophils counts are safe and effective, researchers say.

"Health inequity in cancer treatment and research has many causes, and some are more difficult to address than others. Neutrophil criteria for clinical trials and dose modifications are a hidden contributor to inequity that can be rectified. Now, action to amend these criteria is needed to ensure Duffy-null patients are not disadvantaged," said Hibbs.

More information: Cancer Trial Eligibility and Therapy Modifications for Individuals With Duffy Null–Associated Neutrophil Count, *JAMA Network Open* (2024). DOI: 10.1001/jamanetworkopen.2024.32475

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