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Predicting Hydroxyurea Resistance in Polycythemia Vera with Machine Learning

You're listening to *Project Oncology* on ReachMD, and this is an *AudioAbstract*. I'm Dr. Hallie Blevins, and today, we'll be discussing how to predict hydroxyurea resistance in polycythemia vera using a machine learning technique.

Hydroxyurea remains the most widely used first-line cytoreductive therapy for polycythemia vera, or PV. While many patients typically respond well, a significant number develop resistance or intolerance to hydroxyurea, often within the first year of therapy.

This is closely linked to increased thromboembolic complications, disease progression, and higher mortality rates. Identifying patients at risk of hydroxyurea resistance early in their treatment journey could allow clinicians to proactively switch to alternative therapies, like ruxolitinib, and reduce patient morbidity associated with delayed intervention.

Now, let's dive into some recent research. The 2025 PV Advanced Integrated Models, or PV-AIM, study applied machine learning techniques to a large U.S. real-world dataset, with the goal of predicting hydroxyurea resistance. The research team then launched the prospective Phase four trial, called HU-F-AIM, to validate these findings in clinical practice.

The retrospective PV-AIM study utilized anonymized electronic health records from the Optum® database, which includes data from over 105 million patients across diverse healthcare settings. From this dataset, 1,304 PV patients who had hydroxyurea prescription records, met strict eligibility criteria, and had sufficient laboratory data for model development were identified.

The researchers split patients into two groups: 733 who developed hydroxyurea resistance based on adapted European LeukemiaNet, or ELN, criteria, and 571 who did not show hydroxyurea resistance.

The team developed a Random Forest machine learning model, trained using 80 percent of the data and validated on the remaining 20 percent. Performance was measured by area under the receiver operating characteristic curve, or ROC-AUC, which reached 0.71, and indicates a moderate predictive accuracy.

Key pre-treatment variables were analyzed, including laboratory results, history of thromboembolic events, phlebotomy frequency, clinical observations, demographic characteristics, and use of anticoagulants. The top predictive factors were then tested in combination to identify clinically meaningful thresholds.

The model identified ten critical predictors of hydroxyurea resistance, including hemoglobin, red cell distribution width, red blood cell count, absolute neutrophil count, hematocrit, annualized phlebotomy count, age at index, white blood cell count, patient weight, and time between PV diagnosis and treatment initiation.

In general, higher values were associated with increased risk of hydroxyurea resistance with the exception of age at index. However, the study found a particularly strong interaction between red cell distribution width and hemoglobin. Patients with a red cell distribution width of 17 percent or higher combined with hemoglobin of 15.5 grams per deciliter or lower were significantly more likely to develop resistance to hydroxyurea. In addition, patients with high red cell distribution widths were about 1.4 times more likely to become resistant compared to those with lower values.

This combination enabled the creation of a simple clinical decision tree, where patients can be stratified into four quadrants. Those at highest risk for hydroxyurea resistance are identified by having red cell distribution widths of 17 percent or more and hemoglobin of 15.5 grams per deciliter or lower. These thresholds are easily measurable with standard laboratory tests, offering an accessible tool for early risk stratification.

Further analysis revealed that patients with higher red cell distribution width had elevated white blood cell counts, neutrophil counts, and platelets. Patients also had higher neutrophil-to-lymphocyte ratios, which indicates systemic inflammation.

To confirm these findings, researchers initiated the study HU-F-AIM, which is an open-label, single-arm phase four clinical trial. The study aims to enroll 300 newly diagnosed, hydroxyurea-naïve PV patients, focusing on those who meet the red cell distribution width and hemoglobin predictive criteria.

With these results in mind, early identification of hydroxyurea resistance could support timely transition to alternative therapies and reduce the likelihood of thromboembolic events and disease progression. With simple, widely available lab markers such as red cell distribution width and hemoglobin, clinicians may be equipped to make more proactive, informed decisions that improve patient outcomes and long-term disease control.

This has been an *AudioAbstract* for *Project Oncology*, and I'm Dr. Hallie Blevins. To access this and other episodes in our series, visit *Project Oncology* on ReachMD dot com, where you can Be Part of the Knowledge. Thanks for listening!

Reference

Heidel FH, De Stefano V, Zaiss M, et al. Prediction of resistance to hydroxyurea therapy in patients with polycythemia vera: a machine learning study (PV-AIM) validated in a prospective interventional phase IV trial (HU-F-AIM). *Leukemia*. 2025;39(7):1692-1701. doi:10.1038/s41375-025-02623-5