Advanced parameters offer faster, surer guidance to cancer care

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September 2017—After a career spent studying malignancies in the bone marrow and monitoring the effects of chemotherapy on the bone marrow and neoplastic cells contained therein, Cheryl Hirsch-Ginsberg, MD, stepped out from the bone marrow realm and into the faster-paced world of high-volume hematology.

Thirty-one years ago, explains Dr. Hirsch-Ginsberg, who is a professor of laboratory medicine at MD Anderson Cancer Center, "We would monitor the effectiveness of chemotherapy—both in terms of how well it was clearing and the gradual recovery of the bone marrow—by taking bone marrow from the leukemia patients." But as her research reflects, the extended CBC parameters, including the six-part differential, and the new reticulocyte and optical platelet parameters are proving to be effective tools in evaluating cancer patients, particularly those with hematologic problems. Even though the use of extended reticulocyte parameter profiles is still considered investigational, cancer centers are increasingly relying on this crucial laboratory testing as provided by the XE and XN series of hematology analyzers developed by Sysmex Corp.

At the main clinic of the Cancer and Hematology Centers of Western Michigan in Grand Rapids, for example, the Sysmex XN-1000 system went live in March 2013. The XN now serves 350 patients a day between the main clinic and the centers' three standalone laboratories, which are under the direction of regional laboratory manager Evelyn Graham, MT(ASCP).

As part of the centers' CBC profiles, the Sysmex XN offers five advanced clinical parameters: immature granulocytes (IG, a direct cellular measure of leukopoiesis); nucleated RBCs; immature reticulocyte fraction (IRF, the percentage of cells that are newly released from the bone marrow and are a direct cellular measure of erythropoiesis); reticulocyte hemoglobin equivalent (RET-He, measuring the hemoglobin content of the developing reticulocyte population and an indicator of functional iron deficiency); and immature platelet fraction (IPF, directly measuring the rate of thrombopoeisis). All have helped bring more effective management of cancer patients, Graham says.

The IG parameter has been one of the most significant in this respect. The centers treat many chronic myelogenous leukemia patients, and the Sysmex instrumentation's IG parameter has made it possible for the centers to reduce the number of manual differentials in this patient population by 75 percent. Another benefit of the IG parameter is in patients receiving growth factor drugs like Neupogen or Neulasta, which are used to stimulate white blood cell production. The increased IG count reflects the stimulated white cells released from the bone marrow before fully matured.

However, clinician education was key for the successful use of the IG parameter. The laboratory has opted to report results for CML patients with explanatory canned text, Graham says. It reads: "The IG parameter reflects the combination of promyelocytes, metamyelocytes, and myelocytes." For patients receiving Neulasta or Neupogen, additional canned text notes, "Patient is receiving Neu-pogen or Neulasta which is the most likely cause of the increased IGs."

Automatic reflex testing to obtain an immature platelet fraction has also been a useful tool for clinicians in making platelet transfusion decisions, Graham says. For instance, "With platelet testing, we have the option to do fluorescent platelets, so any time a patient has a platelet count of 50,000 or less, we automatically repeat the platelet count in fluorescent mode, measuring high-, medium-, and low-fluorescing platelets to determine the IPF. The doctors are very happy to have that information."

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Nucleated RBCs, reported in both percentage and absolutes with every CBC, have had a direct impact on workflow, allowing the cancer center to operate more efficiently. “In our practice, the nurses can’t put in orders for chemotherapy until the lab results come back, to ensure all criteria are met.” Patients are assigned to a chair for chemotherapy treatment at a designated time. “So if a chair gets 20 minutes behind while they are waiting for one patient’s results and that continues to happen all day long, there is delay, delay, delay—and it just escalates.”

“Now, with the Sysmex XN, we no longer have to perform time-consuming manual differentials to correct for nucleated RBCs,” Graham says. Instead, the automated results include an accurate absolute neutrophil count (ANC) that serves as the basis for whether to administer chemotherapy that day or not.

Graham is enthusiastic about the faster clinical decisions that advanced parameters like RET-He help provide. “Our responsibility is to provide quick and accurate results to aid the providers in making real-time decisions,” she says. She cites the example of a patient with a slightly low hemoglobin. “The doctor ordered a reticulocyte panel on him and the RET-He result was low. The doctor was able to start the patient on iron therapy much sooner than if he hadn’t had that RET-He result.” On the other hand, when a RET-He is in the normal range, “that parameter guides the doctors to investigate other roads sooner: Let’s check your B12. Let’s check the folate. Let’s see if there’s a GI bleed.”

The immature platelet fraction advanced parameter has proved to be of similar value. “A patient might have a platelet count in the 40s, still at a level where they wouldn’t transfuse. But with an extremely low IPF of only one or two percent, the clinicians would be more proactive in monitoring the patient’s platelet count. They would have that patient come back a lot sooner to get rechecked. Without the IPF, they wouldn’t have known there was a platelet production issue.”

Conversely, since chemotherapy works to kill fast-growing cells, a high IPF or high IRF can show that cells are crossing the bone marrow stroma and getting out into peripheral blood, indicating bone marrow recovery after chemotherapy. Each time a patient gets chemo, Graham points out, the bone marrow takes a little longer to bounce back, so it’s important to monitor recovery. “If you can see what the bone marrow is doing just from that advanced clinical parameter and not have to do a bone marrow biopsy, it’s very beneficial.”

Even though the cost of the XN Sysmex results was going to be slightly increased from the cost of the previous non-XN CBC results, she says, “I could demonstrate to the executive committee the cost-savings benefit. I explained that nurses are going to get their results faster, chemo orders are going to get in pharmacy faster, drugs come out faster, patients get treated faster, patient satisfaction goes up, and overtime goes down. When I showed them those kinds of statistics, they could see that in the long run they would save a lot with the addition of the

advanced parameters."

Integrating the advanced parameters into the centers' laboratory information system was not particularly difficult. "We didn't have any problem with the interface between our Sysmex and our LIS," Graham says, but there were some issues with how the LIS data populated in the patient's EMR. "The doctors were looking at test results in a table format. The ANC was appearing quite a bit lower down in the table, so the doctors weren't seeing it when they were looking at the main page of the report. I had our IT department move the ANC value to populate right underneath the WBC in order for the two results to be viewed simultaneously." They did the same with platelets and the immature platelet fraction. "Once we got those parameters put together, it was much more user friendly for the doctors."

It took some time to get clinicians up to speed on the advanced parameters, but Graham believes the educational effort has been worthwhile. "When you have 20 doctors, I can get in front of each one and say, 'Hey, I want to tell you about our Sysmex; here is the information you're going to see and here is what it means.' Now that they have gotten used to the Sysmex results, they'll call and order a fluorescent platelet or a RET-He on a patient."

She believes advanced parameters will eventually become standard at cancer treatment centers, but some institutions are still lagging in putting the technology to use. "It is my understanding that a lot of places now have this technology but they're not using it or not reporting it, which is surprising. It comes out with every CBC, but they're not releasing the information to doctors even though it expands the patient's clinical picture."

We're all looking for things that will give us a leg up in making a diagnosis," Dr. Hirsch-Ginsberg of MD Anderson says. For her, the Sysmex's six-part differential, separating out immature neutrophils and providing an absolute neutrophil count without having to do a differential, is the No. 1 most critical advanced parameter. "That really was the instrument's main selling point in the first place for us, because clinicians treat or do not treat based on the ANC, and we can provide that to them in a more timely manner now."

In addition, she finds the ability to get an optical platelet as well as an impedance platelet to be helpful in speeding along platelet counts. Results like immature platelet fraction are gaining in importance, but she predicts it will take awhile before IPF is adopted for deciding on transfusion, although, similar to a low reticulocyte count in the face of anemia, it may gain acceptance as a way of predicting secondary acute leukemia. Immature reticulocyte fraction also has promise as a very early indicator, after the onset of chemotherapy, to predict bone marrow recovery, she adds.

In her research, she has been particularly interested in the usefulness of the immature platelet fraction. "Using IPF is much easier than using reticulated platelets and much less invasive than using bone marrow." It's well established that IPF can be used to predict when platelets approach 30,000, she notes. "That has been proven in several different studies in Japan. The problem is they actually transfuse when the patient is at 20,000 platelets. So how well does IPF predict when a patient's level will approach 20,000 platelets? That is a different question." She hopes future studies will test the IPF parameter for this capability using Sysmex instruments.

Researchers have not yet explored the extent to which IPF could influence transfusion practices for cancer patients. "That's only one phase of what you can do with IPF, and it's the phase that's a little harder to achieve," Dr. Hirsch-Ginsberg says. "In order to do a study like that, to answer whether IPF could influence transfusion practices, you'd have to have people committed to not transfusing patients when the platelet counts are below 20,000." Almost all of MD Anderson's patients are treated as outpatients, "and no one is going to send a patient home for three days over the weekend with a platelet count of under 20,000 and not transfuse before they leave the clinic." However, in countries where platelets are less readily available than in the U.S., "you might get a different scenario, because they would then be using risk stratification strategies that may be based on the IPF."

The ability to get an IPF as part of a panel in the same time frame as a CBC, however, makes IPF much more relevant and it's more feasible to perform the studies needed to find the threshold where transfusions could be withheld safely and confidently, she adds.

At MD Anderson, IPF is still not ordered routinely with the CBC. But some researchers and clinicians do place the order. One group that finds the parameter useful is the cardiologists. “We know that despite thrombocytopenia, some acute leukemia patients develop myocardial infarctions. In order to feel confident they can do invasive cardiology safely, the cardiologists are looking at the IPF percentage and absolute number of immature platelets to determine the bleeding risk associated with the procedures.” MD Anderson is also using IPF to identify patients who may be in the early stages of secondary acute leukemia or myelodysplasia (MDS) because abnormalities in the IPF may be predictors for secondary leukemia. Still, these uses are almost all investigational.

Although there are quite a few high-volume hematology analyzers on the market, each with its own strengths and weaknesses, the Sysmex analyzers have gained more penetration into the market and many cancer centers use them, Dr. Hirsch-Ginsberg says. “For one thing, you can get a reliable ANC without a differential count due to the enumeration of immature granulocytes separate from the mature granulocytes.” She considers immature granulocytes an advanced parameter because the automated differential is a six-part differential as opposed to a standard five-part differential. The Sysmex analyzer’s ability to give clinicians that answer quickly, without having to do a manual differential, is important, Dr. Hirsch-Ginsberg says.

Rather than batch the staining of the slides, the Sysmex slidemaker/stainer makes and stains them one at a time, in keeping with lean production principles. In addition, the XE and XN analyzers can be linked in an automated production line with the slidemaker/stainers, she says, allowing hands-off analysis from the time the sample is placed in an analysis rack until it is ready for archiving. “This hands-off approach includes reflex testing for a particular parameter—say, the platelets, where you’re worried about the accuracy of the platelet count.” The XN series automatically takes itself back and can use the optical platelet counting instead of the impedance method of counting. “That’s a very nice feature. The fact that it’s on the line and it reruns itself is very important to us as a time saver,” she says, “as is the fact that the slidemaker/stainers are independent from the other instruments, so you don’t have to rerun the whole CBC to get a thin, machine-made slide.”

While the clinical applications of some of the advanced parameters are not well established, they’re up and coming, Dr. Hirsch-Ginsberg believes. “These are all new things, and people have to test and see where the relevance is. For example, they will help us determine in a CLL patient with thrombocytopenia whether a secondary acute leukemia process is starting or if they are in an ITP situation [idiopathic thrombocytopenic purpura]. That’s where most literature on IPF has been—with the ITP group.” But to get clinicians to order the test is a challenge, she says.

The parameters are not ordered automatically at MD Anderson. Since there are separate CPT codes for the reticulocyte panel and for the IPF, “clinicians have to order everything separately, and ideally they need to link each ordered item to a ‘problem list’ item,” Dr. Hirsch-Ginsberg says. “The reticulocyte panel always includes not just reticulocyte percentage and absolute reticulocyte number but also the RET-He and IRF. So when physicians order that, they get that list. Then it remains partially for the lab, if they have time, and partially for the clinicians to begin to notice those parameters and begin to inquire whether they are useful in their clinical practice.”

“I ask the physicians to order the IPF if I happen to be seeing the CBC and hear they’re worried about thrombocytopenia. They don’t necessarily think of these things, but that’s true with a lot of technology.”

Parameters like RET-He are important for questions of patients’ iron utilization, to help make sure patients’ red cells are adequately hemoglobinized, particularly for renal failure patients who get erythropoetin, Dr. Hirsch-Ginsberg notes. One researcher at MD Anderson is studying the use of the reticulocyte advanced parameters to predict who benefits from additional iron.

“You can have cases—and this is one thing that RET-He can help with—where people have sufficient iron store or even iron overload, but still not sufficient iron for red cell production, because the storage iron is in a form that will never leave the macrophages. Once it’s in hemosiderin, it doesn’t get utilized anymore; it doesn’t go anywhere from there. RET-He can tell how much iron is getting into the red cells, so you get a better idea of whether you have a functional deficit or a real deficit or overload.” These are all measured together by the analyzer and, as a

result, she says, clinicians don't need to take shots in the dark with treatment as often.

Ellinor Peerschke, PhD, FAHA, a specialist in thrombosis and hemostasis, began her study of extended parameters when she first joined Memorial Sloan Kettering Cancer Center five years ago. As vice chair of the Department of Laboratory Medicine, Dr. Peerschke is collaborating currently with the transfusion medicine department to study the frequent blood donor population to identify those with early iron deficiency.

'We need to educate physicians around what the RET-He means, how it can help them.' — Ellinor Peerschke, PhD, FAHA

"The FDA recently put out a guidance for blood collection centers to think about ways to identify repeat or frequent RBC donors to make sure they don't become iron deficient. So we wouldn't wait until the person's hematocrit drops so low that they can no longer donate. Rather, we would look at their RET-He and follow up if it drops or becomes a concern. Then we would ask the donor to defer, recommend a longer interval between collections, so they have the ability to recover their red cell mass, and suggest iron supplements."

This study is made possible because RET-He is a sensitive, rapid test of one of the earliest indicators of potential iron deficiency, Dr. Peerschke says. The RET-He test is also easier to perform than traditional iron studies, which would require another tube of blood for biochemical analysis of serum iron, ferritin, and transferrin saturation. Most important, RET-He is not subject to physiological variations that affect biochemical markers of iron status. "It's a direct measure of the iron available for hemoglobin production in young red cells and provides more relevant information than looking at markers of iron deficiency in the peripheral blood, some of which are acute-phase reactants."

"There is significant information on the use of RET-He and CHr, the RET-He equivalent on the Siemens Advia analyzer, in populations vulnerable to anemia, such as young children and elderly patients, with the goal to easily identify those in need of iron supplementation. At Memorial Sloan Kettering Cancer Center, we extended these studies to cancer patients," she says.

The three major reasons why cancer patients become anemic are bone marrow suppression from chemotherapy, lack of iron utilization because of chronic disease, and iron deficiency, which may be nutritional or due to blood loss. In 2012, the hematology/oncology community issued a recommendation that cancer patients with hemoglobin levels less than 12 g/dL for males and 11 g/dL for females be investigated for anemia. But evaluating iron deficiency in cancer patients is notoriously complex, Dr. Peerschke notes.

Conventional markers are an imperfect gold standard and make interpretation of acutely ill patients' hematology lab results more difficult, she points out. Ferritin, depending on the patient's cancer, may be a tumor marker.

Ferritin overexpression has been observed in hepatocellular carcinoma, Hodgkin's disease, breast cancer, and pancreatic cancer, for example.

"Ferritin and transferrin levels may be affected also by liver dysfunction. So the iron deficiency may be masked."

With a RET-He result, some conditions can be ruled out. "We can very rapidly say that a patient found to be anemic does not have iron deficiency, or poor iron utilization due to inflammation, and conclude perhaps the reason for the anemia is a production defect or the patient may be bleeding. So using this test is less about treatment and more about helping to guide further workups."

Clinicians are still reluctant to use RET-He in isolation to screen for iron deficiency, she finds. "It's not the standard of care, so if you have a low RET-He, clinicians need to go back and make sure they have further evidence of iron deficiency." If the RET-He is elevated, however, iron deficiency can be pretty much ruled out and biochemical evaluations are probably not indicated. "But what we find here, and probably in other hospitals as well, is there are standard order sets for the evaluation of patients, and until those get changed, these workups in the clinical chemistry labs will persist."

To cover some of the bases, Dr. Peerschke's laboratory reports RET-He with an explanatory comment: "If your patient's RET-He is greater than 32 picograms, iron deficiency is ruled out with a fairly high certainty (Negative Predictive Value of 98.5%)." This comment is based on Memorial Sloan Kettering's experience. "It's often the case with lab screening tests that the higher the sensitivity, the lower your specificity. It's a tradeoff, so you need to ask what is your goal." Each laboratory should define its own cutoff, she recommends. "I realize that's burdensome, but if you look at the literature, the cutoffs that are quoted for RET-He and CHr vary. You really need to look at your population."

Her laboratory also recommends that anyone with anemia and a RET-He below 32 pg be evaluated further, and that patients with a really low RET-He may be suspected of having a hemoglobinopathy. "Any time you have decreased red cell production like in alpha or beta thalassemia," she says, "that will give you a low RET-He, often lower than 28 pg."

What would be the impact of eliminating iron studies? "Every lab can look and see what it costs them to do iron studies," Dr. Peerschke says. "Certainly, if you're a very big place and you do a lot of iron studies that tend to be unnecessary, that's a resource utilization issue."

The actual patient impact should also be considered, she notes, because probably all of the patients who come into the outpatient clinic get CBCs drawn. "So we already have a tube of blood, and a reticulocyte count with RET-He is easy to add on. If a patient comes in with unexpected anemia, the clinician can very easily get that first piece of information to decide whether iron deficiency is an issue."

She describes a recent case in which a RET-He helped in a rapid workup of a patient with unexpected anemia. She was a 72-year-old colon cancer survivor who came into the clinic for an annual checkup, and her hemoglobin was down to 10 g/dL compared with the previous year's level of 12 g/dL, which was normal. "Given that she was a colon cancer survivor, there's concern that the cancer has come back, but she denied any rectal bleeding. We were able to provide a RET-He level very rapidly that indicated she did have iron-deficient erythropoiesis. Then the clinician could start to think about how the patient became iron deficient. Is it dietary? Is she bleeding due to cancer but is unaware? The clinician could initiate a further workup pretty rapidly. Otherwise, if you are waiting for clinical chemistry test results to come back from our central laboratory, which take a few hours to come back, the patient would have to be called back for additional diagnostic studies."

Hospitals need a robust education program to properly use RET-He, Dr. Peerschke believes. "We're looking to change clinical practice. The laboratory isn't the one ordering the tests, so we need to educate physicians around what the RET-He means, how it can help them, and, eventually, how it could affect the treatment of their particular patient population. That way, order sets can be rewritten with RET-He as a potential discriminator."

But she is not a fan of rashly adopting a screening test. “We shouldn’t use screening tests blindly in the laboratory to prevent clinicians from ordering tests, unless the screening tests are so robust and they have a negative predictive value of 100 percent.” Instead, Dr. Peerschke recommends, the laboratory should say: “If you don’t have a clinical suspicion and you’re checking because it’s part of your standard protocol to check patients who are anemic with iron studies, then the RET-He may be very helpful in telling you where to focus your energy. If you have a very strong clinical suspicion, by all means do the more definitive tests, and use RET-He to help evaluate those complex patients with inflammation as it may help tease out what the iron studies mean.”

Institutions can develop their own diagnostic algorithms. For example, the RET-He could also be used to reflex to iron studies, hemoglobin electrophoresis, and perhaps even bone marrow analysis, depending on the result. That approach has reflected Memorial Sloan Kettering’s implementation of the parameter for a couple of years now, Dr. Peerschke says.

The general pattern, Dr. Hirsch-Ginsberg says, is that diagnostic tools often stay investigational for a long time before they’re as widely used as they could be. But she and Dr. Peerschke express confidence in the Sysmex advanced parameters’ robustness and their ability to diagnose or rule out hematologic conditions in many populations—the complex cancer population being one of the most important.
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