Blood bank: On guard against daratumumab interference

Anne Paxton

October 2016—As fans of spycraft know, offensive counterintelligence can include an arsenal of strategies: initiating a diversion, sowing confusion, creating false identities—anything that makes another party believe something that isn't true.

If the cancer treatment drug daratumumab were capable of deceptive intent, it might be accused of all those ploys when it comes to interfering with blood transfusion crossmatching. The reason: For patients receiving daratumumab, marketed as Darzalex by Janssen Pharmaceuticals, antibody testing for transfusion is subject to erratic false-positives, often leaving transfusion services confused, uncertain, and on hold.

"The blood bank can't release any blood for these patients, and the transfusion will sometimes be delayed for hours or days while the problem can be figured out," says Richard Kaufman, MD, medical director for the Brigham and Women's Hospital transfusion service in Boston.

Daratumumab was approved by the Food and Drug Administration last year for one application: third-line multiple myeloma treatment. But much wider use of the cancer drug is anticipated soon because trials are showing that it is quite effective. Janssen, a subsidiary of Johnson & Johnson, is working on combining daratumumab with the current first-line myeloma drug, bortezomib (Velcade), for treatment of earlier stage myeloma. And preliminary research findings suggest that daratumumab may work against several other cancers as well, such as B-cell leukemia and lymphomas.

Dr. Westhoff

"There is more widespread use of this drug coming down the pike," predicts Connie M. Westhoff, SBB, PhD, director of immunohematology and genomics at New York Blood Center in New York City. Use of daratumumab for multiple myeloma is "only the tip of the iceberg."

Experts at the nation's top blood centers are sounding a warning in the face of this trend: Without increased awareness and a plan for determining when transfusion candidates are receiving daratumumab, the risk to patient care created by the drug's interference with antibody testing is likely to get worse. "Essentially," says Meghan Delaney, DO, MPH, medical director of the immunohematology and red cell genomics laboratory at Bloodworks Northwest and director of transfusion services at Seattle Children's Hospital, "every blood bank in the country is going to have to deal with this."

When crossmatching is attempted on patients who are taking daratumumab, explains Dr. Kaufman, the antibody screen looks for so-called unexpected (non-ABO) antibodies in the patient's plasma, so the blood bank can ensure that donor red blood cells that are selected for a particular patient will survive normally when transfused to that patient. "The problem with daratumumab is you can't tell if there are antibodies hiding in the patient's plasma because all the testing to detect the antibodies comes out positive. Daratumumab can essentially mask the presence of one or more unexpected antibodies."

This creates a blood bank predicament that is without precedent, according to Dr. Delaney. “There’s no other drug that does what daratumumab does in blood bank testing,” she says. But daratumumab could just be the leading edge of a longer-term problem; other drugs now being tested are similar and could produce the same interference.

Dr. Westhoff agrees. “Monoclonal antibodies used for treatment are becoming much more prevalent, and many of the target antigens are also expressed on red cells, so I see this as a continuing problem, and maybe even becoming a much larger problem,” she says.

The delay caused by daratumumab’s interference with pretransfusion testing and crossmatching is not highly dangerous because the blood is normally not needed urgently. Multiple myeloma patients are mostly being treated as outpatients, not on an emergency basis, Dr. Kaufman says. “Usually they can wait, but sometimes patients come in fairly anemic, and it’s a hassle. It’s certainly a big inconvenience.” However, the delays and consternation the interference causes are unnecessary, Dr. Delaney notes. “If the doctor tells the blood bank that the patient is on daratumumab, then the blood bank could have that information and know to use special testing protocols that get around the problem.”

Multiple myeloma affects a large number of patients; it is one of the more common blood cancers, Dr. Delaney points out. “When the FDA approved daratumumab, it meant that it moved out from the academic centers to wide availability. So community oncologists will now use the drug. It will become much more widespread than just an agent used at big cancer centers.”
problem,” she says.

Daratumumab’s progress to the market as an approved drug has been relatively swift. When Janssen applied for FDA approval, it focused on third-line therapy because it was trying to get a fast approval for the drug, Dr. Delaney explains. Generally, “you first do a study of cases that are multiply resistant to other therapies. And if your drug works, you can get the FDA to approve it for that setting. Meanwhile, right now they are doing multiple other studies to move up in the line, and eventually they want it to become a primary therapy.”
problem,” she says.

It was early in the evolution of daratumumab that Janssen became aware, and clinical trial centers confirmed, that the drug could interfere with blood bank pretransfusion testing. Seattle’s Bloodworks Northwest was one of the centers included in the trials. “We had some patients here in Seattle who were getting the drug when it was still in the trial, and we knew. We were told and then we were working with those samples and giving providers feedback about what we found,” Dr. Delaney recalls.
problem,” she says.

“The big challenge with daratumumab is that this drug is now being given to patients in every hospital everywhere. Yet the only way to know for sure if the patient is on daratumumab or another similar agent is for the provider to inform the blood bank.” That’s not something providers typically do. “They tell the blood bank very little. They prescribe a unit of blood or they order a type and screen, and they don’t tell the blood bank what the patient is on. Nothing magical in that tube lets you know there’s daratumumab there unless they tell you,” Dr. Delaney says.
Janssen has been active in working with blood bank leaders to solve the interference problem, she notes. “Most traditional chemotherapy drugs are chemical agents that are cell killers. They don’t create this kind of interference, whereas the new class of cancer drugs, biologics, are antibodies that are directed at certain targets.”
problem,” she says.

Biologics have been around quite awhile but their toolbox keeps expanding, she points out, and the interference issue has added a new twist to cancer drug development. “Janssen didn’t mean to develop a drug that did this. They just wanted a drug that’s a blockbuster for myeloma. They’ve had to start learning about blood banking, so it’s been a trial by fire. But they’re really engaged in trying to figure out how to let labs handle patients who are on this drug, because they want the drug to be successful.”

When the blood bank tests a sample and finds reactivity with all cells, called panreactivity, the technologists have algorithms for how to deal with that. “But if they don’t know the patient is on daratumumab, they’ll go down the wrong algorithmic branch,” Dr. Delaney points out.

For this reason, the AABB recommends that patients be tested before they begin daratumumab treatment. “This pre-testing, to ensure the patient doesn’t have antibodies to blood group antigens before receiving the drug, sets the stage for the blood bank to be informed. They also can do an extended blood typing, sometimes by genotyping,” she says. When the patient starts the drug and the next sample comes in, “the blood bank technologists look at the record and say, ‘Ah, the patient is on daratumumab.’”

Daratumumab does not interfere with routine blood typing for detection of ABO and Rh antigens. Rather, daratumumab interferes with antibody detection and crossmatching because daratumumab works by targeting CD38, a protein widely expressed on tissues and red blood cells, says Dr. Westhoff.

The presence of the circulating free drug antibody in the patient’s plasma is what causes the confusion during laboratory testing. “In serologic tests, the presence of this drug reacts like an antibody to a high-prevalence antigen. If the blood bank is unaware that the patient has received the drug, time-consuming and complex testing will be undertaken to try to identify the specificity of the antibody present, when in fact the reactivity is not due to a specific antigen that may be lacking on some cells and present on the majority of others. It is directed to CD38, present on all the red cells tested,” Dr. Westhoff explains.

New York Blood Center received its first case with unknown daratumumab interference in June 2014. A large amount of testing was done on the initial case because the reactivity suggested an antibody to a high prevalence antigen. Based on the strength of reactivity, enzyme testing, and the lack of reactivity with cord RBCs, the first suspicion was a Knops antibody. “This was quickly ruled out, and uncommon specificities were investigated using rare RBCs,” Dr. Westhoff says. “Only Lu(a–b–) RBCs of the dominant In(Lu) type did not react, but the very rare recessive type of Lu(a–b–) RBCs did react. The lab was perplexed because we couldn’t believe the specificity could not be identified. It took two additional mystery samples to connect the common diagnosis of multiple myeloma.”

To avoid interference, 0.2M dithiothreitol (DTT) can be used to address the problem serologically. DTT reduces the disulfide bonds in the CD38 molecule on the red blood cells. “The DTT denatures CD38 on the reagent red cells,” Dr. Delaney says.

Bloodworks Northwest performs DTT testing, as do other reference labs, but it’s not routine in most hospital laboratory testing. “So hospitals with patients on daratumumab, when they have interference, will send the tests to us,” says Dr. Delaney. Over time, some hospitals may decide they don’t wish to send out the samples and will bring the DTT protocol into the laboratory if they have the test volume and staff to do it. “But for many blood banks, the DTT chemical treatment is actually a reagent they have to make themselves, it has to be made fresh, and that’s something most hospital blood banks are not interested in doing.”

Another downside of DTT treatment is that, while it reduces the disulfide bond, it also destroys other antigens. “So when you do DTT-treated antibody detection testing, you can’t exclude that the patient has antibodies to the antigens that have been destroyed by the DTT,” Dr. Delaney says, citing Kell antigens as the most common ones to worry about.

Dr. Delaney

“Blood bank technologists need to look out for daratumumab, so if they find a patient with panreactivity, they should flag the case for review or dig around in the electronic medical record, if they have access, to see if the patient has multiple myeloma and the blood bank wasn’t told about the drug order,” she recommends.

Dr. Delaney and many other blood banking experts consider systematic notification to be the most effective approach in dealing with daratumumab interference. “If your hospital hasn’t set up a way to be communicating, for providers or pharmacists to tell you that that patient is going on the drug, that process should be set up.” An automatic alert to the blood bank, when a patient is put on a drug therapy, would be more of an error-proof way to give the blood bank a heads-up, she adds. Many hospitals in the Seattle area have introduced such alerts or other ways of flagging that a patient is on daratumumab, she notes.

But automatic notification to the blood bank about a patient’s drug treatment has never been proposed before, Dr. Delaney says, and while pathologists’ awareness of this need is growing, that awareness is still inadequate. “We had protocols for the drug because our blood bank was a center that was used in the study. When the FDA approved the drug, I got inundated with questions about how to handle this from all different kinds of blood banks—big, medium, and small.” The need for awareness could broaden further if the drug is used in cases of lymphoma or other diseases.

Following the first testing of daratumumab in Europe, Dana-Farber Cancer Institute, which has a large multiple myeloma research group, was part of the phase one and phase two trials of the drug, and became the first site in the U.S. to start using it, says Dr. Kaufman. Brigham and Women’s Hospital adult transfusion service, where he is medical director, serves as Dana-Farber’s blood center.

Dr. Kaufman

Early on, he had discussions with the oncologists engaged in the trials. “There was a little bit of language in the consent form for this research study, saying that there can be some blurring of the antibody screen in the blood bank. It wasn’t clear what that meant or how often you’d see it. But we decided a couple of things. If we saw anything, we’d let oncology know, and we asked for a baseline type and screen before putting anyone on this new drug.”

The first time a patient from the trial appeared and there was this interference, “the techs got really frustrated trying to adsorb it out, and they weren’t able to.” More patients followed “and with all of them, the blood center saw interference. There was basically panreactivity on the antibody screen, so an AHG crossmatch was always incompatible.”

“One thing that was interesting is that we saw some positive DATs [direct antiglobulin tests] and some negative DATs, and other labs started to see this same problem over time,” Dr. Kaufman recalls. “It turned out that most of the time, even though we know the problem is the drug is binding red cells’ CD38, the DAT is negative.”

Neutralizing or using DTT-treated red cells began looking like two ways to address the interference, Dr. Kaufman says. Before Dana-Farber’s experience, a European institution had been working on the interference issue in Utrecht, the Netherlands, and eventually both Dana-Farber and the Dutch group published side-by-side papers on it in Transfusion (Chapuy CI, et al. 2015;55[6 Pt 2]:1545–1554; Oostendorp M, et al. 2015;55[6 Pt 2]:1555–1562).

The Dutch group had been trying a couple of different ways to neutralize the antibody in solution, Dr. Kaufman continues. “One way was to take soluble CD38 protein and mix it in with the patient’s plasma, and the anti-CD38

would bind to that and take care of the problem." A second approach was to take an anti-idiotype, an ITG antibody specific for the F(ab) (fragment antigen-binding) portion of daratumumab. "And that antibody could be mixed up with the plasma. It would bind up the daratumumab and get rid of the interference." He started to believe the problem was most likely that CD38 was expressed at very low levels on red cells.

The normal dose for patients on daratumumab—16 mg/kg—is quite high, Dr. Kaufman notes. "So the idea is that for patients on daratumumab, if the drug is in the plasma, then it will basically stick to the reagent red cells that are used in the antibody screen. Then when you add in immunoglobulin, you get a positive result, usually a weakly positive result. You can't get rid of it as you can an antibody."

"Normally you would use red cells to pull out the antibody so it could adsorb out. The problem with daratumumab is there is really very little CD38 expressed on the red cells, and the ZZAP is what most labs use to do their adsorption—a mixture of dithiothreitol and papain. And we now know that DTT will really efficiently denature CD38."

"So the adsorptions were failing. It was driving people crazy, because in the lab you don't know the patient is on daratumumab. It really can look like an autoantibody or a chemical. You don't know what it is, but you can't get rid of it."

Based on older studies, his blood center ended up using DTT to denature CD38. "Using that approach, we showed you could treat red cells with DTT and get rid of the interference." Trypsin enzyme treatment also works, he adds, but not as well and not as easily. "The main advantage of the DTT method is it is pretty easy and it's very, very cheap." While you can certainly use soluble CD38, he says, "it costs a few hundred dollars to just do the antibody screen, whereas with DTT you can do it and the reagent costs pennies."

However, when the blood center developed this method, conditions were somewhat artificial because the trial was underway. "It was really just the patients on this one study, so we were informed about all patients on daratumumab." Since then, things have changed now that the drug is licensed. "Sometimes we know the patient is on the drug and sometimes we don't. And it can be very frustrating, not just for us but for everyone, if you don't know the patient is taking it."

The laboratory technologists, Dr. Kaufman says, are getting used to daratumumab's quirks. "If they're seeing a weird interference, then they'll just start asking, 'Does this patient have multiple myeloma? Is the patient on daratumumab?'" But the problem won't end there, since daratumumab is now being studied in other diseases. "There are a huge number of clinical trials that are being sponsored by the manufacturer," he points out.

Extended matching"—giving patients cells that are matched based on patient and donor phenotype or genotype—might be another way to avoid daratumumab interference, Dr. Kaufman says. "It's kind of the third approach, after neutralization and denaturation." It doesn't involve dealing with the serology at all, he notes. Some Canadian sites have employed this method, and there may be future interest; however, he believes the most common method to deal with interference right now is through use of DTT-treated red cells. "Extended matching is certainly viable and has its own advantages and disadvantages. It is expensive, but it is another way to handle the problem."

Dr. Westhoff sees extended matching as a promising prevention alternative as monoclonal antibody treatment becomes more common. "To me, this will really drive the field toward prevention of antibody production. Some people become immunized and make antibodies to red cell antigens. But because everybody doesn't, we don't address prevention because of the additional expense."

The only matching done currently is for ABO and RhD, "and we've been doing that since the 1940s," Dr. Westhoff says. "There are 395 other blood group antigens. Not that we would need to match all of them for transfusions, but there are about 12 that are clinically significant, and some are very common."

She thinks these facts make a higher degree of matching between patient and donor, as is done with organ transplants, more practical as a long-term solution when compatibility can't be determined by routine methods. "It's better patient care to actually prevent antibody formation. We have to find a way to afford that in our system," she says.

But Dr. Westhoff believes that will happen because it will eventually be more cost-effective and economical in the future. "All these heroics we are trying to do to demonstrate the absence of blood group antibodies including DTT chemical modification are just not operationally very efficient when we will eventually be able to do better matching genomically by DNA, and with computerization." Because most patients needing transfusion are not in a clinical crisis, she adds, at most donor centers patients can wait 24 hours to get a matched unit rather than a unit off the shelf.

An extended blood group antigen profile, in her view, should be performed on every patient as part of the blood bank record. "That does two things. It allows the clinician or the blood bank to have the choice to do a higher extended match and ask for a donor unit that is an extended match. Second, it allows the blood bank to determine which antibodies the patient is at risk to make, and that's very important information to have. If you have the antigen, you're not going to make an antibody to the antigen."

In the near term, notification to the blood center that a patient is taking daratumumab is "spectacularly important" as a means of addressing the interference problem, Dr. Kaufman says. About half the time, his blood center knows of the drug order and half the time it doesn't know.
"There are something like seven ways to deal with the interference, once you know about it. But you can waste a lot of time and do a lot of work without getting anywhere, if you don't know a patient is on the drug," Dr. Kaufman says.

How can blood centers make notification routine? One measure Dr. Kaufman's blood center is testing is to have an automated alert through the EMR system—in Brigham and Women's case, Epic—to the blood bank if a patient goes on daratumumab. "If a physician orders daratumumab, then we would automatically get a message directly or through the pharmacy to let us know that." But he doesn't believe EMRs are up to this task yet. "I think it's the kind of thing that if you ask for it, you can have it built at your own institution, but I don't think the EMR vendors are really incorporating it in their systems."

Updating laboratory requisition forms to include a query about drugs a patient is taking is another measure that some blood centers are trying. At New York Blood Center, this change has already been implemented, Dr. Westhoff says. "We've seen more than 400 patients on daratumumab here in the last few months. Most of our hospitals are very aware now, so we don't often get surprised. And we've learned to recognize it in the lab now too."

Other blood centers are doing the old-fashioned legwork of making calls to oncology offices to check. Dr. Kaufman notes, at least at academic centers, that if a blood bank technologist sees the diagnosis and finds the antibody screen is positive, "they're often thinking of the daratumumab interference right away at this point." However, he adds, as daratumumab begins to be used for other diseases, "that's where we can run into trouble."

For now, despite the increasing efforts of the manufacturer, researchers, and blood centers to educate providers about the daratumumab interference problem, "What it comes down to is that the pathologists out in the world had better have a conversation with providers," Dr. Delaney says. "If a patient is on daratumumab, the provider needs to tell the blood bank."
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