Coag quest: keying into the clot risk of cancer patients

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January 2015—It's a somewhat stark fact: When hospitalized cancer patients die from something other than cancer, the cause is most likely to be venous thromboembolism. But there is a degree of mystery about why some cancer patients are more prone than others to be afflicted with VTE.

Discovering the reasons, and pinning down the biomarkers that will alert clinicians to the risk, are critically important goals for improving management of cancer patients. Through risk stratification, clinicians can ensure that thromboprophylaxis is initiated for patients at the highest risk of VTE. Recent clinical research is confirming that current clinical guidelines for preventing VTE, based on a risk model called the Khorana score, are on the right track.

But the research also suggests that emerging biomarkers could hone risk prediction even further, enabling more precise early identification of patients at high and low risk of primary and recurrent VTE. After several years of directing the international Cancer and Thrombosis Study (CATS) at the Medical University of Vienna, Austria, Ingrid Pabinger, MD, says, "We are now at the stage of taking all the findings we have and creating an even better risk prediction model than we have now."

Over the past decade, the Khorana risk model for VTE in cancer patients has demonstrated that the risk of VTE in cancer patients increases with certain clinical variables, plus three biomarkers: higher platelet counts and leukocyte counts, and lower hemoglobin. Hospitals' compliance with Joint Commission guidelines for use of the Khorana score has risen significantly in the same period. Now, a flood of research findings is bringing several additional biomarkers on deck, with prospects for improving prevention and treatment.

Alok Khorana, MD, a medical oncologist with the Cleveland Clinic, led development of the widely adopted risk model named after him. He became involved in developing a risk model because of the high rates of cancer complicated by blood clots, and because data emerging in the late 1990s and early 2000s suggested that affecting the coagulation cascade could potentially affect cancer cells.

The Khorana predictive model for chemotherapy-associated VTE includes two patient factors (site of cancer, with the highest risk being stomach and pancreas, and body mass index of 35 kg/m2 or higher) plus three pre-chemotherapy laboratory result ranges: a leukocyte count over 11,000/mm3, hemoglobin level < 10 g/dL, and platelet count of 350,000 mm3 or higher.

Since a CBC is a simple laboratory assay that almost every patient gets, the Khorana risk model is cost-effective as well as practical. (A separate risk model, known as the Ottawa prognostic score, has also been developed for risk stratification of recurrent VTE in cancer patients.)

The Khorana score was proposed and validated with some 4,000 patients in 2008 in a study funded by the National Cancer Institute, Dr. Khorana says (Blood. 2008;111[10]: 4902–4907). Following that paper, other published studies in Austria, Italy, and the U.S. demonstrated that the risk model is effective in predicting risk of VTE in patients with cancer.

When the Vienna group validated the Khorana risk score, they also tested two additional biomarkers: D-dimer and soluble P-selectin. "Similar to CBC, D-dimer is widely available in most hospitals and it was strongly associated with risk of VTE," Dr. Khorana says. The different types of D-dimer assays in different hospitals is the challenge. In addition, "Since most cancer patients have some elevation in D-dimer, it's not quite clear what the exact cutoff should be to predict VTE." But D-dimer is probably the most promising additional marker that could be used, he says.

Soluble P-selectin is a biomarker still considered to be in the investigational category. A cell adhesion molecule identified as an important mediator of the interaction between activated platelets, epithelial cells, and leukocytes, soluble P-selectin also seems to be predictive in combination with high platelet counts. “P-selectin is a very consistent risk marker,” Dr. Pabinger says. But the link has not been validated and P-selectin is not a widely available test.

Factor VIII coagulation factors have proved to be predictive of VTE risk in at least two cohorts of the Vienna CATS study, Dr. Pabinger notes, and another cohort has been confirmed, but those results have yet to be published.

Finally, tissue factor (TF) has been studied by several research groups and also appears promising. Expressed by normal tissues and cells, TF is known to be present on tumor cells, and it has been postulated to have a crucial role in the pathogenesis of cancer-associated VTE.

At the 7th International Conference on Thrombosis and Hemostasis Issues in Cancer, held last May in Bergamo, Italy, an Italian research team reported that in glioblastoma patients, glial-derived TF-bearing microparticles were increased and were significantly associated with development of VTE complications (Radu CM, et al. Circulating microparticles of glial origin and tissue factor bearing in high-grade glioma: further evidence of a prothrombotic role).

Tissue factor assays include IHC grading of TF expression on tumor cells, measurement of TF antigen using ELISA, TF microparticle procoagulant activity, and impedance-based flow cytometry. But in clinical practice, since there is no consensus standard test and TF is generally less available as well, the generalizability of TF results at different hospitals is unclear.

Tissue factor is most significant as a risk marker for pancreatic cancer, one of the cancers most linked with VTE, Dr. Pabinger says. However, “We have no positive results for pancreatic cancer risk reduction when we take into account mortality.” After the research team applied a special statistical method to correct for high mortality in the pancreatic cancer subjects, the risk of VTE ended up appearing lower in people who have advanced disease, Dr. Pabinger says. Further studies are still underway, in part because this result could be misleading. So better confirmation of TF’s value as a biomarker is needed.

Another potential biomarker is prothrombin factor 1+2, which CATS found predicted a twofold increased risk of VTE when levels were elevated, but which has not been validated as a parameter for VTE.

For ongoing clinical research on VTE in cancer patients, Dr. Khorana cites three priorities: identifying better biomarkers or combinations of biomarkers to quickly identify high-risk patients, proving what is the optimum prophylaxis, and identifying the best and most patient-friendly treatment in patients who have already had VTE.

An NCI-funded collaboration recently completed a trial of primary prevention of blood clots in high-risk cancer patients (PHACS) and is now analyzing the data, says Dr. Khorana, who expects to publish the findings this year. “That study included collection of biospecimens before patients received prophylaxis, and there was an observation arm during prophylaxis. So we expect that will yield additional information about these biomarkers.”

In addition, at the December 2014 conference of the American Society of Hematology, findings from a primary treatment study known as CATCH (Comparison of Acute Treatments in Cancer Haemostasis) were presented. “This was a worldwide study of about 900 cancer patients in 40-plus countries and included collection of blood samples on these patients,” Dr. Khorana says. The focus of the CATCH study was specifically recurrence of blood clots, but in six to 12 months he expects to include the CATCH findings in an update of the prevailing risk model for recurrent VTE.

The main obstacle to finding the best biomarkers is the heterogeneity of the cancer population, Dr. Khorana says. “Obviously, not all cancer patients are equal, and it’s also not clear that the pathophysiological mechanism of VTE is the same. There may be different mechanisms for different cancers such as breast or pancreas. And there are

multiple other risk variables including morbidity, obesity, different diseases, how advanced the cancer is, the aggressiveness of the cancer, and the types of treatment the cancer patient is getting. These can all influence the risk." No single biomarker is going to cover everything, he adds.

Cancer treatments such as major abdominal surgery appear to increase patients' risk for a few weeks after the procedure, while some specific therapeutic agents are also risk factors. "Some classes of anti-cancer drugs such as ponatinib and drugs like thalidomide and temozolomide, used in melanoma, are strongly associated with arterial or venous clots. Then there is a class of multi-targeted inhibitors which are associated with primarily arterial clots."

VTE is associated with both short- and long-term mortality, Dr. Khorana explains. "So cancer patients who get blood clots seem to do worse, and they do worse sometimes because the blood clots themselves cause death through a pulmonary embolism or stroke or an MI. And then for some unknown reason, even if they don't die from the blood clots, these patients have worse survival."

He believes that tendency may be related to how coagulation is involved with angiogenesis proteins. "Hypercoagulability may somehow be beneficial for cancer biology in ways we don't fully understand yet. So the hope is that by preventing VTE, we can not only lessen the direct mortality from clots but also improve the odds of benefiting from cancer treatment."

Hospitals vary in how well they implement prophylaxis in patients at risk of VTE, Dr. Khorana notes. "Primary prevention is recommended in the inpatient setting and post-surgical setting. But if you go back five or 10 years ago, we had maybe less than half of patients needing prophylaxis who were getting it. Now the rates are better than they used to be. It's looking like more than 70 percent of patients who need prophylaxis are getting it. But that still leaves about a third of patients who should be on prophylaxis who are not."

A big topic of concern is the best way to treat patients with VTE, he says. "All the studies done so far have been using low-molecular-weight heparins, but those require daily self-injections, which affect cancer patients' quality of life when they are already suffering from chemotherapy and side effects."

"Oral agents seem to hold a lot of promise, because they're once or twice a day pills that don't require injection or monitoring the way Coumadin does. Unfortunately, the oral agents have not been rigorously tested in the cancer population, so we don't know if they're as good as the LMW heparins in preventing blood clots. So there has been some controversy over whether we should start using these newer agents." The Cleveland Clinic will lead a study this year on prevention of VTE in cancer patients using newer anticoagulants such as fondaparinux, rivaroxaban, and dabigatran.

That would change the equation, says Ted Wun, MD, chief of hematology and oncology and associate dean for research at UC Davis School of Medicine. Dr. Wun, who has been doing epidemiological research on the association between various cancers and thrombosis for the past 10 years, says that in currently available formulations, injections of low-molecular-weight heparins are preferred for cancer-associated indications. "The newer targeted agents would be a more convenient way to prevent thrombosis in high-risk patients, and generally more acceptable to patients and their doctors because they wouldn't have to do an injectable every day."

He notes that one intervention trial on ambulatory patients, the PHACS (Dalteparin Prophylaxis in High-Risk Ambulatory Cancer Patients) study, not reported yet, has just been completed. "They identified people with a Khorana score of three and randomly assigned them to a low-molecular-weight heparin versus no low-molecular heparin. The results will be available soon as to whether you can identify a population with a fairly high risk of thrombosis and then, with the intervention, decrease the incidence of VTE by a clinically significant degree."
But this use of the Khorana score isn't quite ready for clinical application, Dr. Wun says. "The studies done so far that have shown an advantage to thromboprophylaxis have been mostly nonspecific. Two very large studies, the PROTECHT [Prophylaxis of Thromboembolism During Chemotherapy Trial] and SAVE-ONCO [assessing the effectiveness of semuloparin for VTE prevention in cancer patients] have shown a significant relative decrease in incidence of first VTE." But compared with the non-treatment arm of the studies, the absolute differences were not

enough for oncologists to adopt widespread prophylaxis.

“Most clinical oncologists don’t think it’s worth it to reduce incidence from essentially four percent to two percent with a treatment that involves an injectable every day for a few months,” Dr. Wun says. Based on surveys of oncologists, there would have to be a higher baseline incidence to make the primary prophylaxis worthwhile. However, because pancreatic cancer patients receiving chemotherapy have one of the highest rates of VTE, it could make sense to target them specifically even without individual risk assessment. “There is a suggestion in both the National Comprehensive Cancer Network guidelines and the American Society of Clinical Oncology guidelines that primary prophylaxis with pancreatic cancer patients might be worthwhile.”

As a clinical decision tool, D-dimer has been in use for a long time in algorithms to rule out deep vein thrombosis or pulmonary embolism, Dr. Wun says. “It’s a clinical score based on certain clinical characteristics such as whether they have cancer, were recently hospitalized, or have a history of blood clots. If they are low risk by these criteria, and have a negative or low D-dimer, the likelihood that they have DVT or PE is very low, and they don’t need to go any further in the diagnostic algorithms.”

Epidemiologic studies at UC Davis as well as other institutions have shown that the stage of cancer also correlates with the risk of VTE. “People who have a more advanced stage of cancer or are getting active treatment are at higher risk of developing DVT and PE,” Dr. Wun says. In addition, tumors that are more clinically and biologically aggressive—either because of inherent tumor characteristics or the stage of the cancer—are generally associated with higher risk. This is true with pancreatic cancer, glioblastomas, and—as UC Davis’ own data have demonstrated—aggressive lymphomas, Dr. Wun says.

These findings have not yet had an impact on routine clinical care or Dr. Wun’s own clinical practice. “I think I’m more prone to giving people who have had an operation and a high-risk cancer more extended thromboprophylaxis. But the data so far is not robust enough to identify a high-enough-risk patient population to routinely give prophylactic anticoagulation in an outpatient setting.”

For inpatients with cancer, clinicians are likely to be much more aggressive about doing routine thromboprophylaxis. “We actually have empirical data to show that. In surveys a decade ago, our rate was very low, but in a follow-up study that we performed in collaboration with four other academic centers, we showed that the percentage of inpatients getting thromboprophylaxis is 60 to 70 percent, which is a big improvement” (Zwicker JI, et al. J Clin Oncol. 2014;32[17]:1792–1796).

“The patients not getting anticoagulant therapy were mostly identified as having some contraindication,” Dr. Wun adds. “So I think that’s been an important change based on some of the research already mentioned.”

There are limitations to the studies that have employed the Khorana score and other markers, he points out. One problem is under- or over-representation of some tumor types, depending on what patients went to a particular clinic and whether samples were available. “So some tumors we see may not be represented in those scoring systems.”

Dr. Wun would like to see a very large and robust study to validate a scoring system that incorporates various lab biomarkers of the hemostatic system, such as D-dimer or thrombin-antithrombin complex, to try to find high-risk groups for VTE. Secondarily, he would like to see studies designed to use the newer targeted anticoagulant agents in both primary and secondary prophylaxis. “This is important from the laboratory perspective, because pathologists may have to bring on newer assays to detect the presence of those drugs and to perform drug monitoring on patients with cancer.”

At the December meeting of the American Society of Hematology, there was a session by coagulation experts on this very topic, Dr. Wun says. “If somebody comes rolling in the door and is supposedly on one of these new drugs, what do we have available to be able to determine if they have the right levels of the drugs?” A number of commercial kit makers are redesigning their coagulation tests to be able to determine the levels of the newer

anticoagulants, he notes. “More and more people will be on these medications because they are more convenient—and associated overall with less bleeding, actually.”

Despite this push, there is a barrier because of the lack of a reversal agent for the newer agents. “Unlike Coumadin or warfarin, where you can give vitamin K and you can give FFP, they’re still working on antidotes,” Dr. Wun says. Some will probably be approved by the Food and Drug Administration soon, but in the meantime, “some people have been hesitant to use these newer drugs” because of that missing piece. Similarly, the best tests for monitoring the drugs’ effects have not been demonstrated. Thomboelastography through hemostatic analyzers like TEG and thromboelastometry through Rhotem are available, “but whether these are good measures for monitoring and reversing the effect of these anticoagulant drugs is really not known.”

More generally, he says, much work remains to be done before new biomarkers can be employed effectively in thromboprophylaxis. “Incorporation of these laboratory-based biomarkers with clinical risk scores has been validated to be predictive of VTE in cancer patients—but not to the point where a group that’s high-risk enough has been identified to be targeted for primary prophylaxis,” Dr. Wun says. “Studies are ongoing with both heparins and the newer anticoagulant agents to determine whether, using a combination of clinical risk score and biomarkers, we can identify a cohort that’s high-risk enough.”

Intriguing discoveries about biomarkers could lie ahead, Dr. Pabinger says, especially in explaining why glioblastomas, which are among the most prothrombotic of malignancies, are different. A study by Dr. Pabinger and Johannes Thaler, MD, PhD, in *Neuro-Oncology* (Biomarkers predictive of venous thromboembolism in patients with newly diagnosed high-grade gliomas. 2014;16:1645–1651) found that lower, not higher, platelet counts were characteristic of patients with glioblastomas who were at risk for VTE. This anomaly is a new finding. “It’s very unexpected. It’s the reverse of what we thought,” Dr. Pabinger says.

Could glioblastoma turn out to be the exception that proves a new rule about cancer patient risk for VTE? Maybe. “Presently we have a very interesting hypothesis about the reason glioblastoma is different, but we have to prove it,” she says. “It’s very clear that the tumor entity—whether it’s pancreatic carcinoma, breast carcinoma, prostate carcinoma, or glioblastoma—is the most important risk factor.”

In the short term, Dr. Pabinger says, “We’ve presented a totally new risk model, and we are working very hard on further research.” She is optimistic that the continuing reanalysis of the CATS data will further refine risk prediction of VTE in cancer patients and help prevent VTE. In her view, “We’re making good progress.”

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