Comment on Ay et al, page 5377

En route to personalized prophylaxis

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Predicting a patient’s outcome reliably is perhaps the one of the most challenging aspects of the art of medicine. In this issue of Blood, Ay and colleagues introduce science to this art by validating the Khorana risk score (the first risk assessment model that predicts how likely a cancer patient is to develop symptomatic VTE) and confirming the value of 2 biomarkers, D-dimer and soluble P-selectin (sP-selectin), as predictors of thrombosis.1

Thromboembolism is a dreaded complication in patients with cancer. Not only does it complicate cancer treatment, it also shortens survival, reduces quality of life, and consumes significant health care resources. Despite therapy with anticoagulants, up to one-third of oncology patients with venous thromboembolism (VTE) will experience recurrent thrombotic events or serious bleeding.2 Primary prevention is the most effective way to reduce disease burden and this is the recommended standard of practice in oncology patients who are hospitalized or having surgery.1 But given that the risk of VTE ranges from 1%–30% among ambulatory patients with cancer and that it varies over time even in an individual patient, a one-size-fits-all solution of providing thromboprophylaxis to all ambulatory patients is unlikely to be beneficial, practical, or cost-effective. In fact, it may cause more harm because of the higher risk of bleeding in patients with cancer. A more sensible and scientific approach would be to identify patients at particularly high risk who would benefit the most from thromboprophylaxis.

So how do we identify this population? Khorana and colleagues first took up this challenge and developed a VTE risk assessment model for predicting the likelihood of VTE in patients receiving outpatient chemotherapy.4 Using registry data collected to evaluate febrile neutropenia and other complications of chemotherapy, they found 5 independent risk factors that predicted for symptomatic VTE during the first 4 cycles of chemotherapy: (1) site of cancer; (2) prechemotherapy platelet count ≥ 350 × 10^9/L; (3) hemoglobin level < 100 g/L or the use of erythropoiesis-stimulating agents; (4) prechemotherapy leukocyte count > 11 × 10^9/L; and (5) body mass index > 35 kg/m². Patients with none of these risk factors had a very low risk of VTE at < 0.8%, while those with 3 risk factors or more, or a high-risk cancer type with 1 or more additional risk factors, had a VTE risk of 7%.

In the Khorana study, some cancers are under-represented and all patients were receiving chemotherapy; data on central venous catheters, use of anticoagulants, and previous history of VTE were not collected. In addition, some experts questioned the validity of the results because thrombotic events were not independently adjudicated and others wondered whether the model is generalizable to unselected patients.

Ay and colleagues provide the answers in this issue.1 They confirm that the Khorana model is able to stratify a broad range of cancer patients into distinct risk groups for VTE using these 5 readily available clinical variables. In the well-characterized cohort of patients in the Vienna Cancer and Thrombosis Study (CATS) that was designed to follow the risk of symptomatic, objectively confirmed VTE, Ay et al report the 6-month cumulative probability of VTE is 17.7% in the highest risk group with a score of ≥ 3, 9.6% in those with a score of 2, 3.8% in those with a score of 1, and 1.5% in patients with a score of 0. In patients with a score of < 3, the likelihood of not having VTE is 94.9%; in the patients with a score of ≥ 3, the likelihood of having VTE is 22.1%.

Ay and colleagues also evaluated whether the addition of 2 biomarkers, D-dimer and sP-selectin, to the Khorana model provides greater accuracy in predicting the risk of VTE. The associations between these markers and VTE were previously demonstrated by the same and other investigators.5,8 Not surprisingly, this expanded model teases out further risk groups. In the highest score group with ≥ 5 risk factors present, 35% of the patients had a VTE event over 6 months, while those without any factors had a VTE risk of only 1%. In patients with a score of < 5, the likelihood of not having VTE is 94.4%; in the patients with a score of ≥ 5, the likelihood of having VTE is 42.9%.

The results are robust yet there are outstanding issues. There are relatively few patients in the high-score (≥ 3) categories, so we are less confident in the estimated VTE risk and the accuracy indices in these groups. The cutoff values used for D-dimer and sP-selectin may not be applicable for different assays. Additional risk factors for VTE, such as distant metastasis, previous history of VTE, use of newer thrombogenic cancer treatments (eg, bevacizumab, thalidomide) were either not significant or not examined in the models. Finally, it is uncertain whether the Ay model offers a clinically meaningful improvement in accuracy that justifies the added complexity and cost.

So, what does this research mean to patients with cancer and the physicians caring for them? Do the models predict the risk of VTE? Yes, they do. Can we reliably use them to recommend thromboprophylaxis in those with a high score? No, not quite yet. Before we use these models to make management decisions about primary thromboprophylaxis, intervention trials must be conducted to prove such strategies are safe and effective. This is important because preventing thrombosis cannot come at the cost of excessive bleeding and the optimal dose of prophylaxis remains uncertain.9 The first clinical trial, funded by the National Heart, Lung, and Blood Institute (www.clinicaltrials.gov no. NCT00876915), is now ongoing to test the efficacy and safety of a low-molecular-weight heparin in preventing VTE in high-risk patients with a Khorana score of ≥ 3 who are starting chemotherapy.

The Ay and Khorana models also raise fascinating questions about the biology of thrombosis in cancer patients. Are the risk factors causally related or simply “bystanders” of hypercoagulability? With leukocytosis, anemia, and thrombocytosis acting as independent risk factors in these models, hematopoiesis or changes in bone marrow milieu may play an important mechanistic role. We still have a long way to go in understanding the mechanisms that govern the interactions between coagulation and tumor biology.

Khorana and colleagues took the first step toward personalizing primary thromboprophylaxis in ambulatory patients with cancer, and Ay and colleagues have propelled us...
further ahead. We are looking forward to the next leap.

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REFERENCES

Comment on Hartigan et al, page 5383

CCR7 alters hematopoietic potential

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Neutropenia remains a major risk factor in the development of invasive aspergillosis (IA) after HSCT. In this issue of Blood, Hartigan and colleagues illustrate that lack of expression of CCR7 on hematopoietic and progenitor cells alters their proliferation and differentiation potential and the cytokine milieu of the lungs leading to a significant reduction in the susceptibility of HSCT recipients to IA.1

IA is an acute and life-threatening fungal disease characterized by severe pneumonia and intense inflammation that affects primarily immunocompromised individuals such as patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). In these patients, mortality from IA can be as high as 80%-90%. Given that anti-IA immunity is predominantly mediated by cells of myeloid origin (although lymphoid-derived cells have been also recognized as effector cells), many attempts have been made to either engineer the stem cell graft to impact the disease or to accelerate myeloid cell differentiation and enhance effector cell production after allogeneic HSCT.2

The role of chemokines in regulating many fundamental processes of hematopoietic cells—including survival, proliferation, differentiation, and migration—is well recognized.3 Chemokine receptors are expressed on a large number of primitive hematopoietic cells as well as differentiated and specialized cells such as T cells.4 These receptors—including CCR7, the target of the investigation by Hartigan et al.—have been detected on murine cells and on different classes of human stem and progenitor cells from different hematopoietic tissues.5 Many chemokines mediate both in vivo and in vitro myelosuppressive effects including CCL19 and CCL21, the ligands of the receptor CCR7.6 Therefore, it stood to reason that CCL19- or CCL21-mediated myelosuppression might be reduced or eliminated if their receptor was not expressed on hematopoietic stem cells (HSCs). This prompted Hartigan and colleagues to examine the reconstitution potential of CCR7−/− HSCs in the context of a transplantation regimen involving the cotransplantation of more committed myeloid progenitors such as common myeloid progenitors (CMPs) and granulocyte-monocyte progenitors (GMPs).

Clearly, 14 days after transplantation, CCR7−/− HSCs reconstituted myeloid effector cells in the spleen and lung of transplanted recipients more efficiently than HSCs from wild-type (WT) donors. Interestingly, however, transplanted myeloid progenitor cells (a mix of CMPs and GMPs) were a minor contributor to the overall pattern of reconstituting myeloid cells at this time point, suggesting that direct stem cell differentiation was responsible for the appearance of these cells in circulation and in these organs. In their experimental design, Hartigan et al challenged transplanted mice with Aspergillus fumigatus conidia 14 days after transplantation, and assessed the presence of donor-derived hematopoietic cells in the lungs of recipient mice (with and without challenge) 2 days later. Before the A fumigatus challenge, and compared with control mice that received transplants with a mix of WT HSCs, CMPs, and GMPs, mice receiving all 3 groups of cells from CCR7−/− mice had significantly higher numbers of total cells, myeloid dendritic cells, macrophages, plasmacytoid dendritic cells, T cells, and B cells. Following the challenge, all these cell types (except T and B cells) increased in number in recipients of CCR7−/− cells and remained significantly higher than in their counterparts receiving transplants with WT cells. Most importantly, 75% of mice receiving transplants with CCR7−/− cells survived the challenge (compared with 100% mortality among recipients of WT cells), and had a less prominent inflammatory response and reduced fungal growth in the lungs. In addition to this altered cellular reconstitution and infiltration into the lungs, recipients of CCR7−/− cells also had a distinct cytokine profile in the lungs after conidial challenge. Analysis revealed that the levels of several proinflammatory cytokines (at both the mRNA and protein levels) were significantly reduced in recipients of CCR7−/− cells while the levels of anti-inflammatory cytokines in these mice were elevated. In head-to-head competition in the same recipient, CCR7−/− cells outcompeted WT cells in the production of dendritic cells in both the lung and spleen. Collectively, these data demonstrate that in the absence of signaling through CCR7, transplanted stem and progenitor cells generate a microenvironment conducive to better control of IA via the production of larger numbers of myeloid progeny and reduced levels of proinflammatory cytokines (see figure).

These interesting and exciting results emphasize the need for both CCR7−/− CMPs and GMPs in mediating the observed protection against IA after HSCT. The exact reason why these classes of progenitor cells are required for the observed pattern of myeloid
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