Using Gene Expression to Predict Recurrence After Surgery in Localized Renal Cell Carcinoma

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- Screening for Malignancy in Patients with Unprovoked Venous Thromboembolism — How Much Is Appropriate?
Using Gene Expression to Predict Recurrence After Surgery in Localized Renal Cell Carcinoma

A deeper understanding of the molecular basis of renal cell carcinoma (RCC) is required to better assess a patient's risk of recurrence after nephrectomy for localized disease. Several markers have been explored in RCC, but none has clinical utility. Our research group sought to identify and validate a novel prognostic gene signature to improve prediction of the recurrence risk of clear cell (cc) RCC, the most common subtype of kidney cancer. Approximately 30 percent of patients treated for localized ccRCC relapse.

By Brian Rini, MD

Dr. Rini is the Director of Cleveland Clinic's Genitourinary Cancer Program and a staff member of the Department of Hematology and Medical Oncology and the Department of Urology. He is a Professor of Medicine at Cleveland Clinic Lerner College of Medicine. He can be reached at rinib2@ccf.org or 216.444.9567.
Methodology and Validation

By analyzing RNA-based tumor gene expression, we characterized a large cohort of patients with localized ccRCC who underwent curative-intent nephrectomy. We created an observational cohort consisting of 942 patients with clinical stage I-III ccRCC who underwent nephrectomy between 1985 and 2003 at Cleveland Clinic and had fixed, paraffin-embedded tumor blocks available. RNA was extracted from the tumor blocks and expression of 732 genes was analyzed using quantitative reverse transcription-polymerase chain reaction. Primary analysis was to evaluate the degree of association between gene expression and recurrence-free interval and was conducted using Cox proportional hazards models. These data resulted in a final list of 11 cancer-related and five reference genes most strongly associated with recurrence. Predominant gene families significantly associated with recurrence (after adjustment for the clinical/pathologic factors and accounting for false discovery) included those responsible for angiogenesis and immune response, in addition to cell cycle and cell adhesion.

Subsequently, we performed a validation study of this gene signature using an independent sample set of 645 nephrectomy samples from Institute Gustave Roussy. The recurrence score (derived from a formula of weighted gene expression results) was associated with disease recurrence (hazard ratio 3.91 for each 25-unit increase in score; \( p < 0.0001 \); see Figure 1). This association remained significant in multivariate analysis accounting for known clinicopathologic parameters.

An Aid for Ongoing Treatment Decisions

This prognostic test in RCC could be highly useful in treatment decisions for localized RCC, especially regarding the management of small renal masses. Additional large-scale efforts are required to further extend such data from prognostic to predictive — that is, investigating whether the identified genes are not only prognostic for recurrence, but also predictive for outcome with currently available systemic therapies in the advanced setting.

Large-scale adjuvant trials are pending with targeted agents and likely in the future with checkpoint inhibitors, and such a test, if predictive, may allow for enhanced patient selection in the adjuvant setting to best balance risk and benefit.

Reference


**KEY POINTS**

Clinically useful biomarkers are needed to assess renal cell carcinoma (RCC) patients' risk of recurrence after nephrectomy for localized disease. Cleveland Clinic researchers analyzed RNA-based tumor gene expression in a cohort of patients with localized clear cell RCC who underwent nephrectomy, to evaluate the degree of association between gene expression and recurrence-free interval. The analysis produced a final list of 11 cancer-related and five reference genes most strongly associated with recurrence. A validation study of this gene signature confirmed its significant association with disease recurrence. This prognostic test could be highly useful in treatment decisions for localized RCC.
Figure 1. Risk profiles of continuous recurrence score (RS) versus five-year recurrence risk by stage in the validation study. The continuous curves showing the association between RS and five-year risk of recurrence were generated with the use of a log-hazard-ratio model stratified by stage (green for stage I and blue for stages II and III) using a 2-degree-of-freedom spline. The dashed curves indicate 95 percent confidence intervals. The dots in the box below the x-axis indicate the distribution of RS by stage.

Figure 2. Forest plot illustrating the performance of gene groups for development and validation studies. Standardized hazard ratios for each group were calculated by dividing the gene expression by the standard deviation (SD) across all patients. The squares indicate standardized hazard ratio point estimates for each gene group, and whiskers are 95 percent confidence intervals.
The Cleveland Multiport Catheter: A New Take on Convection-Enhanced Delivery of Therapeutics to the CNS Yields Encouraging Early Results

Disclosure: Dr. Vogelbaum is an inventor and patent holder of the Cleveland Multiport Catheter (CMC) as well as founder and Chief Medical Officer of Infuseon Therapeutics Inc. He holds equity and royalty interests in these entities. His participation in the CMC's clinical development is covered by a Cleveland Clinic-approved conflict management plan.

By Michael A. Vogelbaum, MD, PhD, and Ghaith Habboub, MD

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Despite exciting progress against many forms of cancer, brain tumors — particularly gliomas — remain one of the deadliest malignancies. Their lethality stems largely from the fact that glioma cells are highly infiltrative in the brain and are resistant to DNA-damaging therapies such as radiation therapy and cytotoxic chemotherapy. These intrinsic cell properties underlie the failure of surgery and radiation, even in combination, to prove curative.

The Challenge: Breaching the Blood-Brain Barrier

Gliomas are also resistant to most targeted anticancer therapies, which lack access to the cancer cells themselves because the blood-brain barrier (BBB) prevents their entry to the brain. Multiple strategies have been tried to at least temporarily open the BBB to allow passage of anticancer therapeutics, but these efforts have not produced clinical benefit for glioma patients. Moreover, attempts to re-engineer therapeutics to enter the brain via known endothelial transporters have yet to see clinical success.

Another approach for improving delivery of anticancer agents to the brain is convection-enhanced delivery (CED), in which therapeutic agents are introduced directly into brain parenchyma via surgically implanted catheters connected to low-rate infusion pumps. While this technique has been in use for nearly two decades, it remains investigational, as no therapeutics have been approved by the Food and Drug Administration (FDA) for infusion directly into brain tissue.

A Fresh Take on Convection-Enhanced Delivery

During the past decades, several large clinical trials identified a need for new CED-specific technology that would more reliably produce successful delivery to the brain. Now a partnership between Cleveland Clinic and the Cleveland-based multinational manufacturer Parker Hannifin Corp. has produced one of the first CED-specific catheter technologies to enter clinical trials — namely, the Cleveland Multiport Catheter™ (CMC).

The Story Behind the CMC

The new technology traces its origins to 2009, when Cleveland Clinic's technology commercialization arm, Cleveland Clinic Innovations, enlisted this article's senior author (Dr. Vogelbaum) to lead a CED catheter development team including biomedical engineers, a patent attorney and a business development officer. The aim was to build on Dr. Vogelbaum's experience with CED in clinical trials and his proposals for multiple new catheter designs.

After extensive work to set design parameters, brainstorm device concepts, and vet the concepts according to patentability and feasibility criteria, the team arrived at a design they called the "cat's paw" concept. It consisted of two microcatheters deployed from the wall of a central catheter implanted in the brain via conventional stereotactic neurosurgical techniques. Initial prototypes were created by Cleveland Clinic's Department of Biomedical Engineering, and functional testing was performed in Dr. Vogelbaum's laboratory using in vitro, ex vivo and in vivo models.

Following successful testing, the device concept was selected for further development by a joint development group formed with Parker Hannifin to commercialize new technologies from...
**KEY POINTS**

Gliomas remain one of the deadliest malignancies due to their highly infiltrative nature and location within the brain, which prevents chemotherapies and targeted anticancer therapies from reaching tumor cells.

Cleveland Clinic has partnered with Parker Hannifin Corp. to develop a novel convection-enhanced delivery device, the Cleveland Multiport Catheter (CMC), which promises a larger volume of drug distribution to the glioma and tumor-infiltrated brain tissue.

Early human testing of the CMC at Cleveland Clinic has confirmed widespread distribution of topotecan and a tracer agent into tumor-infiltrated brain in patients with recurrent high-grade gliomas. While human trials of the CMC for glioma continue, its use for direct brain delivery of therapeutics for other conditions is being explored.
Figure 2. Axial (left), sagittal (middle) and coronal (right) MRIs showing the distribution of infused topotecan and gadolinium in tumor-infiltrated brain 24 hours after the start of infusion via the Cleveland Multiport Catheter. No intravenous contrast was given; the white areas represent the distribution of the infused gadolinium.
HIGHLIGHTS from the
ASH
ANNUAL MEETING
Simple, inexpensive changes in how emergency departments handle cancer patients who present with fever can significantly shorten those patients' wait for antibiotic administration and decrease their hospital stay, a Cleveland Clinic study has found.

The changes involve elevating caregivers' awareness of the urgent nature of febrile neutropenia (FN), and standardizing and accelerating the triage and treatment process.

“It took less than half a year to institute these changes, and their benefits have persisted for years afterward,” says Mikkael Sekeres, MD, MS, Director of Cleveland Clinic's Leukemia Program.

The research results were published online in July in the Journal of Oncology Practice.

A Life-threatening Emergency

FN — defined as an absolute neutrophil count > 0.5 x 10^9 /L and body temperature ≥ 38.3°C, or temperature > 38.0°C for longer than one hour — is a frequent and serious complication of chemotherapy. Mortality rates in excess of 55 percent have been documented in FN patients with multiple comorbidities.

“It's a life-threatening emergency similar to heart attack or stroke,” Dr. Sekeres says.

Findings from randomized clinical trials support early use of broad-spectrum antibacterial drugs to decrease mortality and morbidity in FN patients. Guidelines from the American Society of Clinical Oncology and the Surviving Sepsis Campaign recommend administering the initial antibiotic dose within one hour after triage.

However, there is little data about the quality and value of prompt antibiotic delivery to FN patients in the emergency department (ED), and best care practices for these patients are undefined. Awareness of FN's urgent nature and the immediate need for antibiotic administration is variable among healthcare workers who treat cancer patients.

Since chemotherapy regimens are increasingly delivered in outpatient settings, FN patients are more likely to seek treatment in the ED, where they may encounter treatment delays due to crowding, competition with patients assessed as higher-acuity, and/or inconsistent definitions of and treatment protocols for FN.

Details of the FN Protocol

Dr. Sekeres and his Cleveland Clinic collaborators hypothesized that creating a formal FN pathway would reduce the time to antibiotic administration and produce other benefits.

Their prospective review of medical records of adult cancer patients who presented to Cleveland Clinic's ED with fever identified significant delays in three areas: time from ED registration to physician evaluation, availability of neutropenia testing results and time to antibiotic administration.

In response, the researchers designed and implemented a protocol that:

• Reclassified FN on the Emergency Severity index as the equivalent acuity of a cerebrovascular accident or myocardial infarction
• Triaged FN patients to private rooms at ED registration rather than a communal waiting room
• Standardized the definition of FN at all inpatient and outpatient cancer center and hospital sites

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Febrile neutropenia is an oncologic emergency, and prolonged time to antibiotic administration is associated with increased hospital lengths of stay and poorer patient outcomes.

Cleveland Clinic researchers developed, instituted and tested a febrile neutropenia (FN) education and treatment protocol intended to reduce delays for cancer patients presenting to the emergency department with fever.

The FN protocol resulted in significantly reduced treatment times and hospital stays.
Follow-up research 18 months after initiation of the FN protocol showed that median times to all study end points had continued to decline, with time to antibiotic order down to 22 minutes and TTA reduced to 68 minutes.

“For the first time, we were able to demonstrate that instituting a number of simple interventions decreased the time it took for febrile neutropenia patients to receive antibiotics from four hours to a little over an hour,” Dr. Sekeres says. “With the FN pathway, we were able to decrease length of hospitalization by approximately one day. These changes produced real, lasting value for our patients. They are relatively easy to enact, and could translate to an improved patient experience and reduced healthcare costs.”
For more information, visit clevelandclinic.org/meded.
SLN biopsy is the standard of care for axillary staging in breast cancer. While radiocolloid tracers produce high SLN detection rates, the method is expensive and requires special facilities, equipment and expertise. Near-infrared fluorescence-guided SLN mapping is a promising alternative that enables the surgeon to visualize subcutaneous lymphatic flow in real time intraoperatively.

"Technology continues to develop that allows us to perform fluorescence-guided surgery," says Stephen Grobmyer, MD, Cleveland Clinic’s Director of Breast Surgical Oncology, Co-Director of the Comprehensive Breast Cancer Program and the study’s principal investigator. Although the research focuses on the role of fluorescent indocyanine green (ICG) in women with stage 1 or 2 breast cancer, "in cancer surgery in general this technology may have a bigger role."

In one of the first trials of its kind in the United States, Dr. Grobmyer and his collaborators are comparing ICG with technetium-99m (99m Tc) sulfur colloid radiotracer in women scheduled for lumpectomy or mastectomy. They will compare the number of nodes removed and the proportion that test positive for malignancy using each detection method.

"The best-case scenario for the ICG would be if all the nodes in the study that are cancerous are fluorescent," Dr. Grobmyer says. "So if you have 100 patients, and 30 of those have cancer in the sentinel nodes, ideally in every case that would be picked up by fluorescence."

Traditionally, breast cancer surgeons operate on what they can see at the surface. "With fluorescence imaging, we can see deeper," Dr. Grobmyer says. "If you're looking with your eye, you might not even see a node there. But because the fluorescence can travel up to 1 cm, you can see the glow under the tissue, so you know exactly where to go down and do your dissection."

Shining Light on the Promise of Fluorescence-Guided Breast Cancer Node Detection

Greater surgical precision, equivalent or better sentinel lymph node (SLN) mapping and increased patient convenience — Cleveland Clinic investigators intend to assess these and other potential benefits of fluorescence-guided SLN detection by comparing the new technology with the use of a traditional radiocolloid tracer for breast cancer surgery.
technique, which in some cases appears superior to current techniques,” Dr. Grobmyer says. For example, a study of 821 women found that ICG fluorescence and radioisotope were equivalent in overall SLN detection (97.2 percent and 97.0 percent, respectively). The detection rate for tumor-positive SLN was 93.3 percent for ICG and 90.0 percent for radioisotope. 

Japanese ICG studies also suggest efficacy for detection of hepatoblastomas and use in gastrointestinal surgery to better distinguish bile duct anatomy.

“In the United States, we are in the infancy of using fluorescence to guide cancer surgery,” Dr. Grobmyer says. “There’s a lot we’re going to learn from this trial. This is an example of the future of fluorescence in guiding cancer surgery.”

The study, “Comparison of Use of Indocyanine Green and 99mTc-labeled Radiotracer for Axillary Lymphatic Mapping Patients with Breast Cancer (ICG),” is sponsored by the Case Comprehensive Cancer Center, the National Cancer Institute and Miktaka USA Inc., which supplied the photodynamic eye camera and related equipment. Further trial details can be found at ClinicalTrials.gov.

**Key Points**

- Although radiocolloid tracers are highly effective for lymphatic mapping in breast cancer, more convenient, precise and cost-effective methods would be beneficial.
- In several non-U.S. trials, near-infrared fluorescent solutions injected subdermally have shown promise in visualizing lymphatic flow in real time and enabling sentinel lymph node (SLN) detection for breast biopsy.
- Cleveland Clinic researchers are conducting a clinical trial to evaluate the effectiveness of fluorescence-guided imaging compared with radiocolloid tracing for SLN identification.

**References**

How do you define value-based care?

The standard definition is outcomes over cost, and that is usually measured in clinical outcomes. Increasingly in our cancer center we are focusing on additional outcomes that may be more important to patients — functional outcomes; for example, after a treatment procedure, are you able to carry on normal daily activities? Other outcomes that we are looking at are those we think might reflect on how to manage a patient’s cancer journey. Much of the fear and concern about a cancer diagnosis happens in the first few hours, days and weeks. We are focusing significantly on trying to manage that. One way is to try to speed up how long it takes a newly diagnosed cancer patient to be treated. Historically it takes several weeks for patients to receive their initial therapy.

Why is that?

There are a lot of reasons. The systems tend to be very physician-centric and not so much patient-centric. Not all services are provided in the same location, and not all physicians see patients at the same time. Coordinating care is a challenge. If the initial therapy is a surgical procedure, access to the operating room can be a challenge. If the surgical procedure includes multiple specialties, such as reconstructive surgery for breast cancer, you need to coordinate the availability and schedules of not just the breast cancer surgeon but the plastic surgeon. Another challenge is getting preauthorization from insurance companies to have certain procedures done. One of the striking things is that academic medical centers do worst among all healthcare providers on this time-to-treat metric — significantly worse than do community cancer centers. So there’s an enormous opportunity for us to improve that, and I think we will.

How can you reduce time to treatment?

You do what we call value-stream mapping. We use business intelligence tools to try to tackle the issue. You start with access points. In an organization like ours, there are many access points for a patient to enter our healthcare system. If a woman has a breast mass, there are many different locations where she might receive a mammogram, an MRI or a biopsy. Once you identify those, you look at all the steps to the initial treatment. As an example, patients with lung cancer almost universally need to see a cardiologist to make sure that they are fit and can have a surgical procedure in their chest. We have to address all those steps one by one to see what we can do to become more efficient and how to coordinate care better. The first step is to acknowledge that it is a priority, and to have everyone involved talking to each other.

Is delivering value-based cancer care more challenging compared with other diseases or medical specialties?

Cancer is a very complicated disease. We are learning more and more that the genetics of an individual can play a role in the development of cancer. For the cancers in which we have good outcomes, treatments tend to be relatively standardized, although there is always some variation. But because many diagnoses are not associated with favorable outcomes, that opens up a lot of different ways to try to approach treatment, from chemotherapy to genomic therapy to immunological therapy. We believe that creating cancer treatment pathways or treatment algorithms is a way to approach
better than the standard of care. And trials allow us to develop them, implementing them and keeping them current.

What role does patient communication play in value-based care?

For the newly diagnosed patient, in addition to time to treatment, it is important to measure the time from knowledge of a diagnosis to when a patient sees a physician. Another metric is how long it takes for the patient to talk to anyone on the cancer team. We are going to adopt a more robust patient navigation program and a care coordination program so that we can make both of those two very important metrics as short as possible. The key is to link the patient with care professionals who give a consistent message. Inconsistent messaging is one of the things that can be very confusing to patients. A truly integrated program, in which surgeons, radiation therapists, medical oncologists, radiologists and pathologists all agree on the best way to treat a patient, allows for consistency of messaging. We can also do that by adhering to care paths, and by having tumor boards to discuss cases as a group.

In a standardized, value-based system, is there a place for innovative treatment approaches?

Absolutely. We have to try to cure cancer. That is what academic cancer centers are here to do. And that means we have to be involved in science, which of course has to be structured within approved clinical research protocols. But our first option is always to try to enroll patients in a clinical trial. That is essential in all value-based care. Any ethical clinical trial is going to be as good if not better than the standard of care. And trials allow us to learn. We want to make sure that the things we measure and define as value are meaningful to patients. You have to ask them. We are actually going to do more of that — use focus groups and talk to people about what matters to them.

How have caregivers responded to the value-based approach? Has it been difficult to get people to buy in?

It has been surprisingly easy, and the concept has been embraced by virtually everyone. One concern when we were starting to construct our care paths was that they were designed by our experts on the main campus, but at some point we had to introduce them to physicians in our regional facilities and to other practicing physicians. We wanted their feedback: Did the care paths seem reasonable and practical in the community setting? What was missing? We were concerned that they might view the care paths as too prescriptive or too academic. In fact the exact opposite was true. They welcomed the care paths and felt that we could be as specific and as prescriptive as we wanted to be. The field of cancer is exploding in terms of our knowledge of causes and treatment options. So our physicians very much appreciate having a care path for a given diagnosis that is based on current evidence.

Value-based care depends on controlling costs and making care affordable as well as efficient. The cost of new cancer drugs is soaring. How can you deal with that?

That is a complicated issue. Many cancer center leaders are very concerned about the cost of cancer drugs, especially the newer kinds — the targeted therapies and immunological therapies. There is not an easy way to fix that because we want to have new drugs that work. Care paths help, so we are very evidence-based when we construct our treatment algorithms. As an example, we have shown that in lung cancer, if we avoid using a newer drug that really has not shown much efficacy, we can drive tens of thousands of dollars out of the cost of care for a given patient. But every member of the cancer community who looks at value-based care is very concerned about the cost of newer cancer agents. There is no easy answer to that right now. There is a lot of political maneuvering. A petition signed by many cancer experts suggests that these drugs may be more expensive than necessary. In Canada they might cost half as much as they do in the United States, and in Europe they might cost even less than that. So clearly there are market forces at work. I think the healthcare continuum has to learn how to work together more effectively. Instead of insurance companies, the pharmaceutical industry and healthcare providers such as Cleveland Clinic being three very large and separate silos, we all need to figure out how to work together so that everyone wins. Ten years ago the cost of a new cancer drug for a course of therapy was $10,000. Today, it is closer to $150,000. And the concern is obvious: Ten years from now, is it going to be $1 million? That is not a sustainable model. So rather than having us get in the ring and do battle, somehow we have got to figure out how to work collaboratively.
Aplastic anemia is a rare bone marrow failure disorder in which patients' immune cells turn against stem cells in the bone marrow and damage blood production, resulting in anemia, a lack of platelets responsible for blood clotting, and a lack of white cells responsible for immune defenses.

Aplastic anemia has been considered a nonmalignant condition, although a small percentage of patients progress to a myelodysplastic syndrome and/or acute myeloid leukemia. Clinicians have had difficulty predicting which aplastic anemia patients are at risk for these blood cancers. Researchers have now identified gene mutations in some aplastic anemia patients that are associated with progression to malignancy. Though more research is needed, the mutations in myeloid cancer candidate genes may trigger the immune response that results in aplastic anemia, and may also help protect mutated hematopoietic cells from immune-mediated destruction, allowing them to further proliferate.
Aplastic anemia is widely accepted as an autoimmune disease in which destruction of bone marrow hematopoietic stem and progenitor cells by the immune system leads to pancytopenia. The later development of MDS, AML or both in some aplastic anemia patients has been termed clonal hematopoiesis or clonal evolution, although there is evidence of this process in patients who do not progress to leukemic conditions. The origin and dynamics of clonal evolution in aplastic anemia and its relationship to the development of MDS and/or AML has been unknown.

Dr. Maciejewski and colleagues at Cleveland Clinic; the National Heart, Lung, and Blood Institute; and Japan's Kanazawa, Kyoto and Nagoya universities and the University of Tokyo used advanced genetic analysis to study the clonal hematopoiesis process in aplastic anemia. The investigators performed next-generation genetic sequencing and array-based karyotyping on a total of 668 blood samples from the 439 study participants. They chose 106 genes for targeted sequencing, including genes in which mutations were already associated with myeloid cancers.

Almost half the patients with aplastic anemia in the study showed evidence of expanded hematopoietic cell clones, and about one-third had acquired mutations in candidate genes for MDS and/or AML. Clonal hematopoiesis in the study participants usually manifested as somatic mutations in a few known MDS/AML driver genes — DNMT3A, ASXL1, BCOR and BCORL1.

In total, the researchers identified 249 somatic mutations in 156 patients (36 percent of the study population). About one-third, or 56 of these 156 patients, were found to have multiple mutations. With few exceptions, the presence and number of mutations per patient significantly correlated with increasing patient age.

Clinical Associations

In a subset of patients with severe aplastic anemia, the researchers tested blood samples after the patients underwent six months of immunosuppressive therapy. Overall, they found no association between the presence of mutations and response to treatment. However, when they examined the mutations individually, two mutations (of BCOR and BCORL1) were associated with a good immunotherapy response.

Although more research is needed, good overall survival was associated with the presence of these “favorable” somatic mutations. In contrast, hematopoietic clones carrying mutations in DNMT3A, ASXL1 and a few other genes were more likely to increase in size over time, and these gene mutations as a group were associated with a reduced response to immunosuppressive therapy, poorer overall survival, and progression to MDS and/or AML.

Even so, overall survival and progression-free survival rates did not significantly differ between patients with and without somatic mutations.

A Theory and Unanswered Questions

The discovery of the mutations in myeloid cancer candidate genes could help explain both the immune response and the progression to MDS/AML in some aplastic anemia patients, Dr. Maciejewski says. Although the exact pathogenesis is unknown, in these cases, clonal hematopoiesis may represent the earliest stages of leukemogenesis. The presence of certain mutations may initiate the immune response that results in aplastic anemia. And some mutations may help protect mutated hematopoietic cells from immune-mediated destruction, allowing them to further proliferate.

“This might support the still unproven theory that what makes the immune system destroy our own bone marrow in aplastic anemia is the appearance of these mutations,” Dr. Maciejewski says. “This is one of a few examples of a benign disease in which leukemogenic mutations have now been detected.”

The researchers include a caveat with their findings. “Despite the association of particular gene mutations observed early in the course of disease with the response to therapy and survival, it should be underscored that the complex dynamics of clonal hematopoiesis are highly variable and not necessarily determinative.”

More research on the pathogenesis of aplastic anemia is warranted, Dr. Maciejewski says. “Why is it that some of these clones that cause leukemia in aplastic anemia actually go away, versus some that invariably lead to leukemia?” Future investigation could uncover which mutations drive subsequent leukemia and which ones remain just neutral passenger mutations.
Lymphomas are among the more difficult malignancies to understand, with a complex classification system. Until recently, from a clinical standpoint I was a "lumper," simply considering a lymphoma as indolent or aggressive. Now we must all become "splitters," as enhanced understanding of the molecular genetic pathophysiology of various lymphoma subtypes impacts prognosis and treatment.

A Diverse Family of Diseases

Diffuse large B cell lymphoma (DLBCL), the most common lymphoma subtype and the prototype for aggressive lymphomas, is now recognized as a family of diseases with different genetic drivers. Most DLBCLs are categorized as either germinal center (GC) cell or activated B cell (ABC) subtypes. The good news is that we continue to cure a high percentage of DLBCL patients with the standard chemotherapy combination of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R–CHOP). The not-so-good news is that the ABC subtype has a poorer prognosis than does GC. Accurate characterization of the ABC or GC subtype relies on gene expression analysis that has not been routinely available. Immunohistochemistry (IHC) is an available but imperfect surrogate.

Our Cleveland Clinic pathology colleagues have developed a polymerase chain reaction-based multigene assay that we now routinely utilize to assign subtype when making new diagnoses of DLBCL. 1 A nonoverlapping prognostic categorization depends on \( \text{MYC} \) and \( \text{BCL2} \), either at the gene rearrangement or protein expression level. Both genes are chromosomally translocated (usually t(8;14) for \( \text{MYC} \) and t(14;18) for \( \text{BCL2} \)) in the relatively uncommon (~ 5 percent) "double-hit" DLBCL. Double-hit DLBCL patients have poor outcomes with R-CHOP, and we usually treat them instead with the dose-adjusted regimen of etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R).

More common are "dual-expressors" — DLBCL patients who are IHC-positive for both \( \text{MYC} \) and \( \text{BCL2} \), but without translocations. Though outcomes for these patients are not optimal, R-CHOP remains the standard treatment. Novel research approaches are in development.

Testing Drug Combinations

Does ABC versus GC subtype affect treatment? Not yet, but soon. ABC-DLBCL is driven by the NF-\( \kappa \)B pathway, a prime target of proteasome inhibitors such as bortezomib. Several randomized studies comparing R-CHOP with or without bortezomib in DLBCL have been completed, with more results expected soon.

One issue is excess neuropathy due to the combination of bortezomib with vincristine. Cleveland Clinic is conducting a phase 1 and 2 trial of initial DLBCL therapy combining R-CHOP with the non-neurotoxic proteasome inhibitor carfilzomib (an approved drug for myeloma). The current dose-finding cohort permits all DLBCL subtypes, while the expansion cohort will focus on the ABC subtype. The GC subtypes do quite well with current therapy, but look for trials combining epigenetic or \( \text{BCL2} \)-inhibiting agents with R-CHOP for these patients, based on biological insights gained from gene expression and genetic analyses.

More Targeted Trials

Despite generally favorable outcomes for DLBCL, as many as 30 to 40 percent of patients relapse and require additional therapy. In fact, as fewer patients relapse after initial therapy, outcomes for those who do relapse are worse.

There is no standard therapy for patients who relapse after, or who cannot undergo, dose-intense chemotherapy with stem cell support. We are investigating novel approaches for such patients.

Reference


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Patients whose DLBCL carries a mutation in the MYD88 gene (commonly altered in Waldenstrom macroglobulinemia) — which can be tested in previously biopsied tissue even before the patient requires therapy — are eligible for a dose-finding study of IMO8400. This oligonucleotide, administered subcutaneously twice weekly, blocks Toll-like receptor (TLR) signaling through MYD88.

For the majority of patients without MYD88 mutation, we offer selinexor, a first-in-class selective inhibitor of nuclear export (SINE) that binds to the nuclear pore to prevent passage of growth regulatory proteins into the cytoplasm, inducing cytotoxicity. It is attractive mechanistically and because it is an oral agent.

Cleveland Clinic is about to open three additional studies of novel agents. One study uses an antibody to PD1 (which is well-known from recent approvals in melanoma and lung cancer as a means to restimulate T cells to attack cancer) to treat patients with relapsed DLBCL. The other two use antibody-drug conjugates (ADCs), which target a cytotoxic drug directly to cells expressing the target of the antibody. This strategy has been highly effective against CD30-expressing lymphomas. These two ADCs each target a different antigen — either CD19 or CD37 — expressed almost exclusively on the surface of some normal B cells and almost all B cell lymphomas.

Immune Stimulation and CAR-T

Stimulating the immune system to kill malignant cells has been a long-sought goal that is only recently showing broadly applicable efficacy. Antibody interference with PD1/PDL1 interaction to re-energize existing tumor-specific T cells is one exciting approach. Bispecific antibodies such as the anti-CD19-CD3 antibody blinatumomab harness nonspecific T cells to bind to CD19-expressing lymphoma/leukemia cells.

Another approach is to insert a chimeric antigen receptor (CAR) into T cells (CAR-T) so that, when re-infused, they will be activated upon binding to the tumor cell. The CAR-T cells currently in use for lymphoma have a single transmembrane protein in which the external domain binds to CD19 and the internal domain contains T cell activating and coactivating domains.

Logistically, a patient undergoes a single leukapheresis to collect T cells, which are then engineered into CAR-T, a process that takes 7 to 10 days in the lab. Meanwhile, the patient undergoes relatively mild lymphodepleting chemotherapy, followed by CAR-T re-infusion. The main toxicity is often an acute, transient cytokine release syndrome that occurs about one week post-infusion.

Cleveland Clinic is conducting a clinical trial of CAR-T cell therapy in patients with relapsed DLBCL.

Summing Up

In conclusion, standard cytotoxic chemotherapy combinations (R-CHOP front-line and high-dose at relapse) are effective and will remain important components of therapy for DLBCL. Targeted approaches are moving quickly into the clinic, however, including agents targeting intracellular processes, surface molecules and the immune system.
New Building Supports Expanded Cancer Research Capabilities

While the $276 million building that will be the new home for the Cleveland Clinic Cancer Center is designed to optimize patient care, it will also significantly enhance cancer research capabilities.

“There will be ample space for our scientists to collaborate with our clinicians,” says Taussig Cancer Institute Chairman Brian J. Bolwell, MD, FACP. “The best way to conduct clinical research is to enable the different components of a disease-based program to share ideas. In melanoma, for example, it is important that plastic surgeons, medical oncologists and dermatologists work side by side and collectively agree on what the next clinical investigation will be. Our new building will facilitate that cooperative approach.”

The six-floor, 377,000-square-foot facility, which will house outpatient cancer treatment, patient support services, medical imaging, radiation and chemotherapy, and physician and administrative offices, will open in 2017.

In addition to multidisciplinary treatment spaces, the new cancer building will have dedicated areas for phase I, II and III clinical trials. There will be special emphasis on supporting phase I trials, making possible a considerable expansion of that program.

“Phase I trials are important for the drug development process and give patients access to novel therapies that wouldn’t otherwise be available,” says Dale R. Shepard, MD, PhD, FACP, Director of Taussig Cancer Institute’s Phase I Program. “The new building will help the growth of this program.”

“We participate in, and often lead, clinical trials of exciting new drugs and radiation and surgical approaches that are only available at a few select centers,” says Mikkael Sekeres, MD, Director of Cleveland Clinic’s Leukemia Program and Vice Chair for Clinical Research at Taussig Cancer Institute. “The new home for the Cleveland Clinic Cancer Center will support multidisciplinary teams of medical oncologists, surgeons and radiation oncologists who will collaborate to select the best standard approach or clinical trial, based on individual patient needs.

“Medical teams will meet with patients under one roof, within a building that will also house dedicated pharmacists who specialize in standard and experimental therapies, laboratories for sophisticated testing, research nurses who specialize in specific cancers, and study support personnel,” Dr. Sekeres says. “All of that will ensure that patients receive outstanding medical care.”

The new cancer building’s basement will hold an expanded, redesigned area for radiation oncology services, including Gamma Knife® radiosurgery treatments. “The whole radiation therapy unit is being remodeled, and that will provide an enormous opportunity to significantly expand our radiation therapy research,” Dr. Bolwell says.
A fairly common patient presentation is of so-called unprovoked venous thromboembolism (VTE): development of a deep vein thrombosis or a pulmonary embolism without a clear provocation, such as major surgery or trauma. Surprisingly, despite considerable advances in our understanding of the etiology of VTE, such unprovoked episodes can account for as much as 40 percent of all VTE cases, thereby representing tens of thousands of events annually in the United States.

Addressing the Question of Screening Thoroughness

The linkage between cancer and VTE is well-known. Cancer cases account for at least one-fifth of all VTE cases, and cancer is an important and established provoking factor for VTE. Therefore, it is reasonable for a case of unprovoked VTE to raise concerns about undiagnosed cancer as an underlying factor.

But if a cancer diagnosis is not immediately apparent — say, cough and hemoptysis identified on review of systems — how thoroughly (and expensively) should physicians search for occult underlying malignancy? And does a thorough search truly impact patient outcomes?

These are questions addressed in a large randomized Canadian study recently reported in the *New England Journal of Medicine,* about which I was privileged to provide a commentary.

**Study Details**

Carrier and colleagues assigned more than 800 patients to undergo either limited occult-cancer screening (basic blood testing, chest radiography and age-appropriate screening for breast, cervical and prostate cancer) or limited occult-cancer screening in combination with an enhanced computed tomography (CT) abdominal scan that included a virtual colonoscopy and high-resolution pancreas imaging.

Among the randomized patients, 3.2 percent in the limited-screening group and 4.5 percent in the group receiving limited screening with enhanced abdominal CT were found to have occult cancer within a 12-month follow-up period.

In primary outcome analysis, four occult cancers (29 percent) were missed by limited screening, whereas five (26 percent) were missed using enhanced screening. Neither of these differences was statistically significant. There were also no significant differences in time to a cancer diagnosis (approximately four months in both arms) or in cancer-related mortality (about 1 percent in both arms).

Encouragingly for patients, the risk of subsequent cancer was therefore quite low. The authors concluded that adding enhanced CT of the abdomen and pelvis to routine age-appropriate screening did not provide significant benefit.

One weakness of the study is the mean age of its cohort (53 years), because cancer is much more likely to occur at older ages. An open question therefore is whether an older population would have led to different results.

**Screening for Malignancy in Patients with Unprovoked Venous Thromboembolism — How Much Is Appropriate?**

By Alok A. Khorana, MD

Dr. Khorana is the Director of Cleveland Clinic's Gastrointestinal Cancer Program and a staff member of the Department of Hematology and Medical Oncology. He can be reached at khorana@ccf.org or 216.636.2690. On Twitter: @aakonc

**References**

However, it is not uncommon for study participants to skew younger than general populations—certainly the study population did not limit accrual by age, and this still represents the best randomized data in this setting thus far.

Doing More versus Doing the Right Thing

For clinicians, the bottom line is that “doing more” does not appear to identify more cancers in patients with unprovoked VTE and certainly does not affect cancer outcomes. Doing more can also increase radiation exposure, lead to unnecessary interventions to follow up on false-positive results and engender patient anxiety.

Value is an important proposition in the care of patients in the current healthcare environment. In this particular setting, less is more. Limiting workup for occult cancer in unprovoked VTE to age-appropriate screening is the right thing to do for our patients.

**KEY POINTS**

Undiagnosed cancer can sometimes be the underlying cause of unprovoked venous thromboembolism (VTE). That raises the question of how extensive cancer screening in cases of unprovoked VTE should be, and what impact varying levels of screening may have on patient outcomes.

A recent study found that the prevalence of occult cancer was low among patients with a first unprovoked VTE, and that routine screening with abdominal and pelvic computed tomography did not provide a clinically significant benefit.

A limited approach to malignancy screening thus appears prudent.
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