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WINTER 2016
Defeating cancer means attacking it from every angle, from conducting the basic research needed to better understand tumor biology to helping our patients make choices that improve their odds of survival. The size and complexity of the challenge requires a multifaceted effort, with each subspecialist contributing his or her unique expertise.

In this issue of Innovations in Cancer, we explore the diversity of expertise available at University Hospitals Seidman Cancer Center – and how our disparate parts make for an even greater whole.

Our cover story focuses on our approach to genomics, including efforts by Christopher Hoimes, DO, Joseph Willis, MD, Afshin Dowlati, MD, and Shaveta Vinayak, MD. Dr. Hoimes, who heads our Genomics Tumor Board, is Principal Investigator at UH Seidman Cancer Center of the NCI Match trial, the largest effort to date for understanding the landscape of genomic alterations in tumors, as well as our ability to impact patients’ disease course. To support this and other work, Dr. Willis and the pathology team at UH Case Medical Center have simplified the genomic testing process. Their new “hotspot” panels identify mutations in up to 50 genes at a time, using a single tumor specimen. At the same time, Dr. Dowlati and Dr. Vinayak are putting genomics to work for their patients, using the information to provide proven targeted therapies for lung cancer and spare some women with early-stage breast cancer the rigors of chemotherapy. They’re also active in the lab, identifying new molecular targets for non-small cell lung cancer and exploring the overlapping molecular irregularities between triple-negative breast cancer and breast cancer caused by BRCA mutations.

Another area of strength at UH Seidman Cancer Center is our stem cell transplant program, headed by Marcos de Lima, MD. In our feature article, Dr. de Lima discusses the aggressive approach that he and his team have used to triple the number of investigator-initiated, locally developed therapeutic clinical trials available to patients with hematologic malignancies.

A multifaceted cancer program also addresses how patients’ lifestyle and health care choices can affect outcomes. To that end, Cynthia Owusu, MD, is exploring how exercise can improve survivorship for older women after breast cancer treatment, especially African-American women and women of low socioeconomic status, who tend to have poorer breast cancer outcomes. And Robert Abouassaly, MD, provides some needed clarity on how to advise patients about prostate cancer screening, in the wake of the controversy over changing guidelines.

The articles in this issue of Innovations in Cancer highlight just a few of the many different approaches we employ at UH Seidman Cancer Center. But they represent our commitment to fighting disease on every front, with all the tools at our disposal.

Warm regards,

From the Director

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Asa and Patricia Shiverick – Jane Shiverick (Tripp) Professor of Hematologic Oncology, Case Western Reserve University
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Prostate Cancer Screening: What Do We Know Now?

UH Seidman Cancer Center urologic oncologist advocates for active surveillance

In the wake of changing guidelines related to prostate cancer screening, a newly published review article from University Hospitals Seidman Cancer Center provides important guidance about the prostate specific antigen (PSA) test.

“While PSA screening has reduced prostate cancer mortality, it is not very accurate and has led to overdiagnosis and overtreatment,” says Robert Abouassaly, MD, a urologic oncologist at UH Seidman Cancer Center. “Because prostate cancer can be slow-growing, we recommend active surveillance.”

To reach their conclusions, Dr. Abouassaly and urologic oncology colleague William Tabayoyong, MD, PhD, conducted a thorough review of recent large-scale studies and assessed the impact of shifting guidelines related to PSA screening. The investigators found that active surveillance can reduce the harms of overtreatment in prostate cancer, publishing their findings in the peer-reviewed journal Surgical Clinics of North America.

The investigators focused specifically on two large, randomized trials assessing the effect of PSA screening on prostate cancer: the Prostate, Lung, Colorectal and Ovarian (PLCO) trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial. The PLCO trial did not show a significant reduction in prostate cancer mortality between the screening group and the usual care group. The ERSPC trial demonstrated a significantly reduced rate of prostate cancer mortality by 20 percent after nine years of follow-up, with a number needed to screen of 1410.

Specifically, Dr. Abouassaly and Dr. Tabayoyong’s review of current data found that active surveillance can reduce overtreatment by almost 50 percent at 15 years. Further, they found that men on active surveillance are not at immediate risk of death from prostate cancer if therapy is deferred until the cancer progresses.

“Widespread use of PSA screening led to a decrease in mortality from the disease; however, the screening may have led to overtreatment of clinically insignificant cancers,” Dr. Abouassaly says. “Although PSA has been validated as a prostate cancer marker, the screening test’s accuracy is limited. It is not specific for prostate cancer and cannot discriminate between low-grade versus high-grade disease.”

In 2012, citing evidence that the risks of prostate cancer screening outweighed the benefits, the U.S. Preventive Services Task Force (USPSTF) released a statement recommending against its use. The USPSTF made this recommendation based on the negative results of the PLCO and the high number needed to screen reported by the ERSPC. This decision was met with concern from professional organizations, including the American Urologic Association and Society for Urologic Oncology. The groups warned that this was a disservice to men that would result in failure to prevent avoidable deaths.

In their review, Dr. Abouassaly and Dr. Tabayoyong found that since the release of the USPSTF statement, the use of PSA for prostate cancer screening has dramatically declined. They point to a recent survey of patient attitudes on prostate cancer screening. It found that although a majority of patients were in favor of prostate cancer screening, after reading a document based on patient education materials from the American Urological Association in favor of screening and then reading another document based on patient education materials from the USPSTF opposing screening, 13 percent of patients changed their minds and adopted a less favorable opinion of screening.

Dr. Abouassaly and Dr. Tabayoyong also point out that while complete abandonment of PSA screening will eliminate all cases of overdiagnosis, it will also fail to prevent 100 percent of avoidable cancer deaths.

“Currently, active surveillance is a feasible strategy to reduce overtreatment without compromising the therapeutic window and chance for cure,” Dr. Abouassaly says. “Future efforts should emphasize strategies to distinguish between clinically insignificant and aggressive prostate cancers so that definitive therapy can be disseminated appropriately.”

For more information, email Robert.Abouassaly@UHhospitals.org.

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Genomic profiling provides valuable information about the potential molecular vulnerabilities of a particular cancer. However, even in experienced hands, it can be unwieldy and slow.

“Up to this point, technologies haven’t allowed us to analyze more than a couple of genes per tumor sample,” says Joseph Willis, MD, Division Chief of Clinical Pathology at University Hospitals Case Medical Center. “We needed a platform where we could use just a small amount of tumor DNA and get a large amount of information.”

Such a system is now in place at UH Seidman Cancer Center. Developed in conjunction with the Department of Pathology at UH Case Medical Center and Case Western Reserve University, the new “hotspot” panel tests can identify mutations in up to 50 genes at a time, using a single tumor specimen.

“We’ve initiated this at UH Seidman for colon cancer, gastrointestinal stromal tumor, melanoma, uveal melanoma and acute myeloid leukemia,” Dr. Willis says. “Our intent is to continue to roll this out for other tumors.

“The idea is to identify more molecular targets than we were previously able to do with one specimen,” Dr. Willis adds. “But it’s more than that. There are other different platforms that can be used in synergy with these tests, such as fluorescent in-situ hybridization (FISH). The idea is to use these other ancillary tests in tandem with the next-gen sequencing to come up with a better profile of the tumor. This will help us better predict how the patient is going to do and identify different therapies that the patient may be able to use.”

Patients at UH Seidman Cancer Center who have stage 4 disease may undergo genomic testing, typically after one line of standard therapy. These results are reviewed by a Genomics Tumor Board, which makes recommendations. The breast cancer group within UH Seidman Cancer Center also has a dedicated genomics tumor board.

“Several medical oncologists, as well as geneticists, pathologists and other tumor board registrars, are present and we discuss the best opportunities for targeting the cancer,” says genitourinary medical oncologist Christopher Hoimes, DO, Chair of the UH Seidman Genomics Tumor Board. “There are many alterations in cancer. It takes a genomics tumor board to distinguish the driver mutations and those that can be acted upon with molecular therapy. A mutation may occur, but it may not be the linchpin driving the process.”
Patients who have cancers known to be responsive to molecularly targeted drugs also undergo routine genomic testing. Lung cancer patients, for example, get genomics “when they walk through the door,” Dr. Hoimes says.

“Genomics has more implications in lung cancer than in any other cancer at this point,” adds Afshin Dowlati, MD, Director, Thoracic Oncology Program at UH Seidman Cancer Center. “There isn’t another disease that’s even halfway there in terms of targeted therapies. There are at least six to eight genomic abnormalities in non-small cell lung cancer. Non-small cell lung cancer comprises 90 percent of all lung cancer, and these genomic abnormalities affect 20 to 25 percent of patients. We have specific targeted therapies against these mutations, either available now or through clinical trials, so it’s relatively huge.”

Genomics also plays a critical role in the care of UH Seidman Cancer Center patients with breast cancer. Patients who have early-stage, hormone-receptor-positive disease undergo genomic testing to predict their need for and response to chemotherapy.

“This test includes an analysis of 21 different genes and provides a composite score of how overproduced or underproduced expression of these genes is,” says UH Seidman Cancer Center breast cancer specialist Shaveta Vinayak, MD. “For women shown to be at high risk, their treatments include chemotherapy and hormone therapy. The low-risk women can be spared chemotherapy.”

Like other patients with advanced disease, women with metastatic breast cancer also undergo genomic testing. Women with aggressive triple-negative breast cancer typically are tested after just one line of chemotherapy, Dr. Vinayak says.

“We look ahead to see whether there are targeted therapy options for those patients,” she says. “The test reveals the DNA changes in the tumor, we get those results back and discuss them in our Breast Genomics Tumor Board.”

In addition to integrating genomics into clinical care, the team at UH Seidman Cancer Center is also involved in both basic science to understand tumor behavior and the more applied area of early drug development. UH pathologist Dr. Willis is a member of the team that discovered the unique genomic signature of colon cancer among African-Americans, published in the Proceedings of the National Academy of Sciences. At the same time, breast cancer specialist Dr. Vinayak is pursuing the overlapping molecular irregularities between triple-negative breast cancer and breast cancer caused by the BRCA mutations.

“Understanding the biology of triple-negative breast cancer and BRCA1- and BRCA2-mutant breast cancer allows for improved therapeutic strategies that target the DNA repair defects of these tumors,” she says. “Trials with treatment selection based on tumor DNA repair capacity in triple-negative breast cancer are currently in development and may lead to improved long-term outcomes.”

On the drug development side, Gries Endowed Director for the Center for Cancer Drug Development, Dr. Dowlati and his team have mined genomic and drug-sensitivity data in the Cancer Cell Line Encyclopedia and Cancer Genome Project to identify new therapeutic agents for small cell lung cancer (SCLC).

“There are currently no molecular, targeted approaches to treat SCLC, similar to those used successfully against non-small cell lung cancer,” Dr. Dowlati says. “We’ve identified heat shock proteins, cyclin-dependent kinases and polo-like kinases (PLK) as attractive molecular targets. Using PLK inhibitors as an example, we identified and validated a gene signature for drug sensitivity in SCLC cell lines. This gene signature could distinguish subpopulations among human SCLC tumors, making it very useful clinically.”

For his part, genitourinary medical oncologist Dr. Hoimes is capitalizing on the fact that cancer may be treated based on genomics as opposed to site of origin. Genomic alterations are seen across many different types of cancer, and using a precision medicine approach to treat these patients based on their tumor’s genomics while on a clinical trial is showing promise. Dr. Hoimes is also exploring how genomics information can inform host anti-tumor immune responses with potential to use more sophisticated agents such as anticancer vaccines, checkpoint immunotherapy and adoptive cell therapy.

“We’re starting to break down the idea that cancer is relegated to any particular histology or tumor type or organ type,” he says. “At least for some cancers, there may be a crossover. We currently have a handful of ‘basket trials’ using molecular targeting agents in patients with specific mutations found in their tumor and agnostic to the cancer site of origin. The broadest basket is the NCI Molecular Analysis for therapeutic choice (match) trial at Case Comprehensive Cancer Center. As PI of the NCI MATCH study at UH Seidman Cancer Center, we’re looking for patients who have genomic alterations and matching them to a drug that can potentially interrupt the genomic driver alteration. This is the largest effort that we’ve had for understanding the landscape of genomic alterations in tumors, as well as ability to impact patients’ disease course. Because the tumor site of origin is not a factor, this trial has really broadened the population of patients able to be considered for a trial and has been especially exciting for those with rare cancers.”

For more information on genomics at UH Seidman Cancer Center, email Christopher.Hoimes@UHhospitals.org.

All National Institutes of Health (NIH) funding for basic and clinical research is awarded to the School of Medicine at Case Western Reserve University.
After stem cell transplant (SCT), cure rates for hematologic malignancies among adults hover between 30 and 50 percent. For Marcos de Lima, MD, these disappointing numbers represent an invitation to innovate.

“For the vast majority of these diseases, there simply are no standards of care,” says Dr. de Lima, Director of the Hematologic Malignancies and Stem Cell Transplant Program at University Hospitals Seidman Cancer Center. “There are silver standards, but not gold standards. Given this situation, our commitment is that the best treatment is often a clinical trial.”

Since arriving at UH Seidman Cancer Center three years ago from M.D. Anderson Cancer Center in Houston, Dr. de Lima and his team have tripled the number of investigator-initiated, locally developed therapeutic clinical trials available to patients with hematologic malignancies. These trials focus on three broad goals of the program: finding donors for every patient who needs a donor cell transplant, reducing the toxicity of the SCT process and reducing relapse rates.

“Unfortunately, relapse after transplant is still a huge problem,” Dr. de Lima says. “It’s one of the great paradoxes of our field. Over the last 20 years, the toxicity of transplants has gone down. The tradeoff is that we see people whose disease comes back more readily.”

To address the challenge of a lack of matched donor cells, Dr. de Lima is embarking on a pilot project combining donor cord blood cells with mesenchymal stromal cells (MSCs) harvested from a volunteer unrelated to the donor or recipient. To avoid the problem of cells that get ‘lost’ in the bloodstream, he and his team are injecting these cells directly into patients’ bone marrow. The MSCs are injected into the bone marrow immediately before the cord blood.

“We’ve seen that if we combine human cord blood cells with MSCs from an unrelated human and inject the combined cells into a recipient mouse’s leg bone, we see better engraftment with more donor cells remaining in the marrow,” Dr. de Lima says.

A trial with 10 to 12 patients, using this approach, is now under way at UH Seidman Cancer Center, with the first patient receiving treatment in late 2015.

“Ultimately, if it does succeed, it could challenge the standard of care, which is currently to do a double cord blood transplant,” Dr. de Lima says. “What we’re proposing is a complete shift.”

Another trial under way within the program is tackling the tradeoff between toxicity and relapse, which can be a special problem for older patients with hematologic malignancies. Because of age and reduced overall health, these patients often receive what Dr. de Lima describes as “reduced intensity transplants” or “mini transplants,” which may leave them vulnerable to relapse.

“We’re investigating whether we can add radiation to the standard transplant for older adults,” he says.

The twist is that the radiation is delivered only to the skeleton, using sophisticated body mapping and total marrow irradiation (TMI) technology, sparing the lungs and other tissues.

“You avoid more toxicity to the lungs, for example, so theoretically, you’re taking away some of the side effects,” Dr. de Lima says.

Making SCT as safe as possible for patients is also a key priority, Dr. de Lima says. This manifests itself in both research and clinical care. On the research side, he and his team are investing in laboratory bioreactors that will allow for the cultivation and selection of subsets of cells to attack cytomegalovirus (CMV) in SCT recipients.

“CMV is a pest after transplant,” Dr. de Lima says. “Sometimes we have a hard time treating it with drugs. The idea is that we’ll be able to separate lymphocytes from a donor that only recognize this particular virus, so you can give the cells without risk of side effects. They’ll just attack the virus.”

Clinically, the team is committed to standardizing procedures where possible and making nurses experts in certain pieces of what can be an involved SCT process.

“There is a lot of engagement by the nursing staff, which is vital to our success,” Dr. de Lima says. “When they become knowledgeable, they become partners and another check on the process. You want as many checks as possible in this huge process that we have.”
Over the past few years, the link between exercise and breast cancer survivorship has become increasingly clear. Studies have shown that women who engage in regular physical activity after a diagnosis of breast cancer have reduced recurrence and mortality, when compared with breast cancer survivors who don’t exercise regularly.

However, most of these studies have been done in younger women. “There’s a paucity of data on older breast cancer survivors,” says Cynthia Owusu, MD, a geriatric oncologist at University Hospitals Seidman Cancer Center. “Furthermore, studies of exercise involving older African-American and socioeconomic status-disadvantaged breast cancer survivors, two groups that are particularly vulnerable, are lacking. This has been identified as a critical research need.”

To address this issue, Dr. Owusu has secured a $2.8 million grant from the NIH’s National Institute on Minority Health and Disparities, awarded to the Case Western Reserve University School of Medicine, to study how physical activity affects functional status, body composition and known biomarkers associated with breast cancer among survivors over age 65. The project has a special focus on older African-American women and women of low socioeconomic status.

“It’s an established fact that African-American women and women of low socioeconomic status tend to have poorer breast cancer outcomes,” Dr. Owusu says. “In a recent study that looked at breast cancer survival in older women, older African-Americans were twice as likely to have poorer outcomes, compared with their Caucasian counterparts.”

Dr. Owusu suspects that this disparity is driven, in part, by differences in functional status at the time of breast cancer diagnosis. In research published in the journal Cancer in 2013, she and colleagues reported that functional disability is very common among older women diagnosed with early-stage breast cancer, with older African-American women disproportionately affected.

More recently, Dr. Owusu led a group of national colleagues in reporting that more than 40 percent of older adults with cancer are considered functionally disabled at the time they begin chemotherapy. This research was published in the Journal of the National Comprehensive Cancer Network (NCCN).

For the new project, Dr. Owusu and colleagues from other Cleveland-area health systems are recruiting 320 women age 65 and older who completed treatment for early-stage breast cancer no more than two years ago. They’re identifying four subgroups of 80 women each: Caucasian women of high socioeconomic status, Caucasian women of low socioeconomic status, African-American women of high socioeconomic status, and African-American women of low socioeconomic status.

Within these groups, women are being randomly assigned to an intervention of 150 minutes per week of structured aerobic and resistance exercise, attended at a local cancer support organization, or a once-a-week health education session. After 20 months in the structured exercise program, research participants will be asked to create their own fitness schedule.

“We’re interested whether 20 months of a structured exercise program helps them establish their own program, whether it influences their habits,” Dr. Owusu says.

Dr. Owusu’s team will also gather data on participants’ body mass index, body fat composition and waist circumference and will conduct observational tests of functional status at baseline, 20 months and 52 months. In addition, they will take measurements of known biomarkers associated with breast cancer, such as sex hormones, insulin and C peptide, among others.

Dr. Owusu says she’s excited about the potential of this project to help this underserved group of breast cancer survivors. In a pilot project, which she and colleagues described in the Journal of Physical Therapy and Health Promotion in late 2013, breast cancer survivors who’d completed treatment within the past year and who participated in the structured, 20-week exercise program had significantly lower levels of circulating C-peptide by the end of the program.

“Obese patients tend to produce more of these biomarkers, so they stand to benefit the most from exercise,” Dr. Owusu says. “We think these could be reduced with exercise and weight reduction, therefore protecting them from breast cancer recurrence.”

For more information on this project, email Cynthia.Owusu@UHhospitals.org.
A recognized authority on cancer and health care economics, Neal J. Meropol, MD, is a member of the American Society of Clinical Oncology’s Value in Cancer Care Task Force, charged with defining the value in cancer care by clinical benefit, toxicity and cost. The task force recently published its proposed value framework in the Journal of Clinical Oncology and invited public comment. Dr. Meropol is also the principal author of Preparatory Education About Clinical Trials (PRE-ACT) on the patient information website Cancer.net. PRE-ACT, an interactive, video-based program, is designed to boost participation in cancer clinical trials and help patients make personalized treatment choices.

Sanford Markowitz, MD, PhD, is co-recipient of a new, three-year, $600,000 grant from the Stuart Scott Memorial Cancer Research Fund, created by the V Foundation, to discover why some cancers are more aggressive and more fatal in African-Americans. The new fund made grants to only three institutions nationwide. Dr. Markowitz and his team first described novel colon cancer mutations among African-Americans, publishing their findings in the Proceedings of the National Academy of Sciences. They’ve also found that people with high levels of the protein 15-PGDH in the colon cut their risk of developing colon cancer in half by taking aspirin. Dr. Markowitz leads the Specialized Program of Research Excellence (SPORE) in Gastrointestinal (GI) Cancers for Case Comprehensive Cancer Center.

Thoracic oncologist Afshin Dowlati, MD, is a leader in genomic research addressing small cell lung cancer (SCLC). He and his team have identified a new mutation in SCLC called RET, publishing their findings in the Journal of Thoracic Oncology. They’ve discovered that the RET protein is sensitive to two new targeted therapies, ponatinib and vandetanib. Dr. Dowlati is also a previous recipient of the National Cancer Institute’s Michael C. Christian Oncology Development Lectureship and Award, which recognizes the contributions of individuals to the development of novel agents for cancer therapy.

Mitchell Machtay, MD, is one of America’s leading developers of radiation oncology clinical trials, focusing primarily on lung cancer, brain tumors and head and neck cancer, particularly in combined modality therapy for moderately advanced disease. Dr. Machtay was national principal investigator of a lung cancer study demonstrating that PET-CT scans following combination chemotherapy and radiotherapy predict long-term outcomes. Dr. Machtay was also one of the first radiation oncologists to use taxane chemotherapy during head and neck cancer radiation therapy and one of the first to use pemetrexed chemotherapy during lung cancer radiotherapy. These are now commonly used, safe and effective approaches toward these diseases.