Cleveland Clinic

Cancer Advances

Cleveland Clinic Cancer Center | Winter 2017

The **Future** of **Cancer Care** is **Here**

Ranked No. 8 in America for cancer care by *U.S. News & World Report*.

Dear Colleagues,

It is an exciting time at Cleveland Clinic Cancer Center.

Our new cancer outpatient tower is nearing completion and will open in March. This $276 million, 377,000-square-foot building is the result of years of planning and incorporates everything we have learned about the delivery of compassionate, highly accessible multidisciplinary care.

It will allow us to consolidate all cancer services — medical and surgical consults, chemotherapy and radiotherapy, diagnostic imaging, phase I clinical trials, hematology laboratory, pharmacy, a wellness center and other patient and family support programs — in a single location designed for maximum convenience. Expansive windows, skylights, open floor plans and extensive artwork will make for a serene, uplifting setting.

While aesthetics are important for patients' state of mind, the paramount thing we can do to ease their anxiety is to treat their cancer as quickly as possible. As you will read on page 24, we are among the first institutions in the nation to intensively track and comprehensively improve our time-to-treat intervals. Co-locating our caregivers and services in a central location certainly will help in this ongoing effort.

Timely treatment must be grounded in high-quality research, and there is much good news on that front as well:

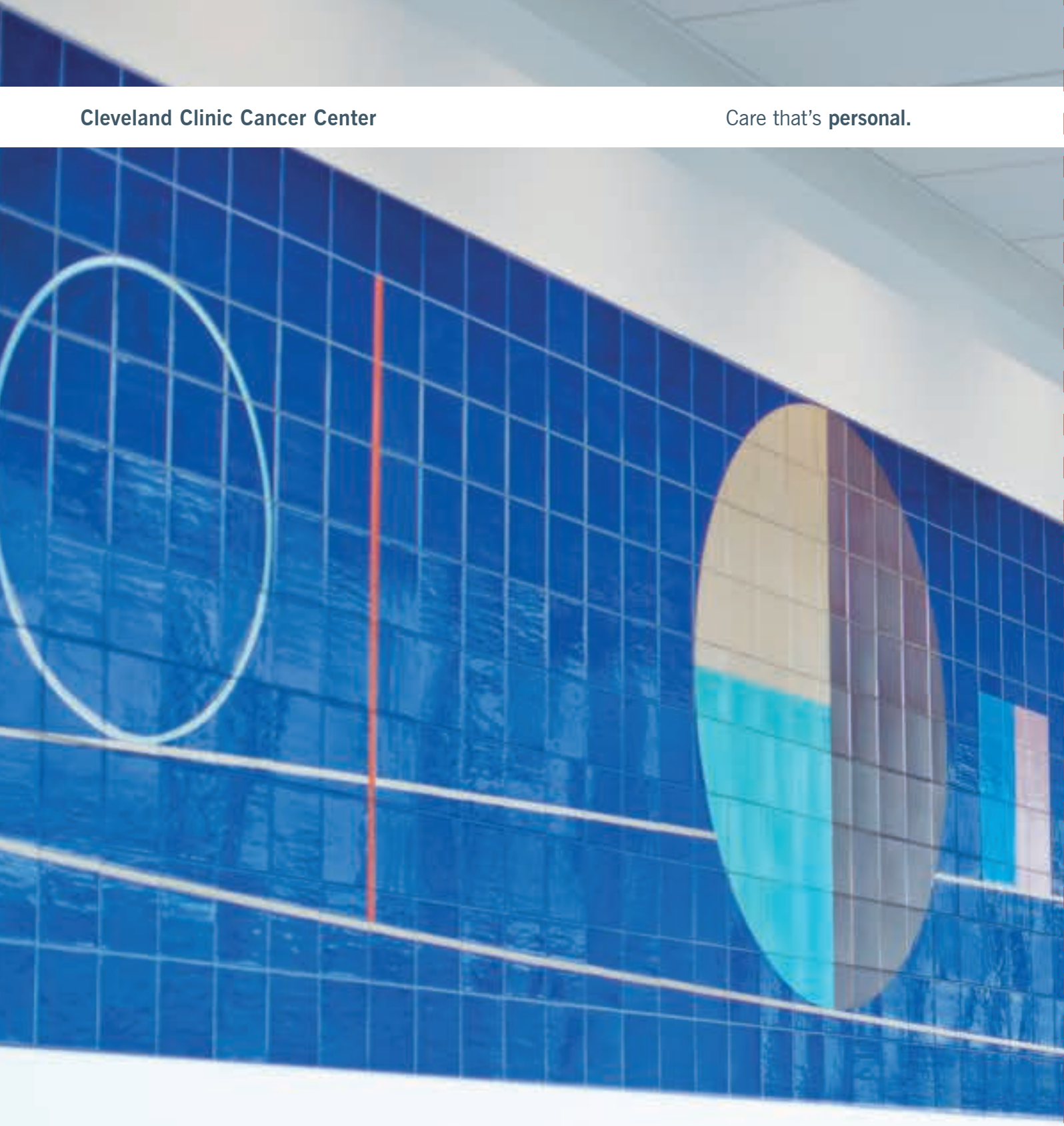
The newest member of our Translational Hematology and Oncology Research team, Jacob Scott, MD, (see P. 9) brings a new field of research to Cleveland Clinic Cancer Center. Mathematical oncology has the potential to reveal essential principles that govern cancer biology, which could point the way to new, more effective treatments.

The third annual VeloSano cycling fundraiser in July 2016 collected $3.4 million for Cleveland Clinic Cancer Center research. Nearly 1,600 riders pedaled more than 81,000 miles, making this the most successful VeloSano to date and bringing its three-year total to more than $8 million.

In the pages that follow, you can read more about the breadth and depth of research underway at Cleveland Clinic Cancer Center. I am proud of these and other projects that are redefining cancer care. As always, I welcome the opportunity to collaborate. Our Cancer Answer Line staff at 866.223.8100 is ready to help you with patient appointment referrals, clinical issues and other information. And our site for cancer clinicians, Consult QD/Cancer (clevelandclinic.org/ConsultQDCancer) provides timely oncology insights and perspectives from our experts.

Sincerely,

Brian J. Bolwell, MD, FACP
Chairman, Taussig Cancer Institute
Cleveland Clinic Cancer Center
bolwelb@ccf.org | 216.444.6922
On Twitter: @clebmt



Claudia Wieser, Sculptures, 2016, glazed ceramic tiles. Site-specific commission for Cleveland Clinic Taussig Cancer Center.

Research that's **revolutionary.**

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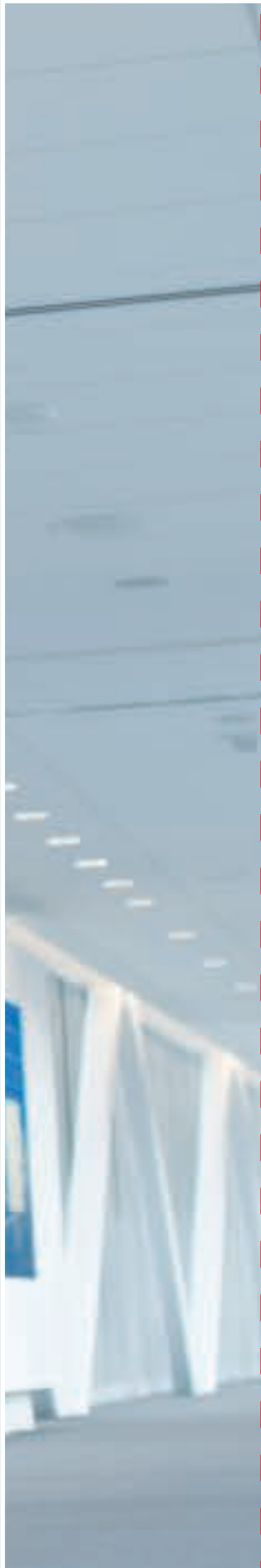

Studies Advance the Understanding of Androgen Synthesis and Inhibition Strategies in Aggressive Prostate Cancer

Cleveland Clinic oncologist Nima Sharifi, MD, has spent years investigating androgen metabolism and its part in the evolution of metastatic castration-resistant prostate cancer. In 2016 Dr. Sharifi published the results of two significant androgen-related studies that have the potential to impact prostate cancer treatment. Following are details of each project.

Dr. Sharifi is a staff member in Cleveland Clinic's departments of Hematology and Medical Oncology, Cancer Biology, and Urology. He holds the Kendrick Family Endowed Chair for Prostate Cancer Research and is Associate Professor of Molecular Medicine at Cleveland Clinic Lerner College of Medicine.

He can be reached at sharifn@ccf.org or 216.445.9750.

On Twitter: @NimaSharifiMD

Fine-Tuning Anti-Androgen Therapy Shows Promise

Armed with new insights into how metastatic prostate tumors gain resistance to the next-generation androgen inhibitor abiraterone, Dr. Sharifi discovered a way to make the drug's activity more durable and potent.

Pairing abiraterone (abi) with the enzyme inhibitor dutasteride modifies abi's metabolic conversion, blocking production of a tumor-promoting metabolite while aiding accumulation of another metabolite with strong antitumor effects, Dr. Sharifi and colleagues reported in *Nature*.

"These findings hold enormous potential for changing the way abiraterone is prescribed to patients," says Dr. Sharifi, the study's senior author. "While more work is needed to determine the ultimate clinical effect of biochemically altering abiraterone metabolism in this way, our team has identified a promising new combination therapy that stands to improve the care of men with metastatic castration-resistant prostate cancer."

Probing Androgen Metabolism

Prostate cancer is the second most commonly diagnosed cancer and the second leading cause of cancer deaths in American men. Last year, most of the estimated 26,100 prostate cancer deaths in the U.S. were due to metastatic castration-resistant disease.

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Advanced prostate cancer initially regresses following gonadal testosterone deprivation therapy (either medical or surgical castration) but eventually recurs. This happens in large part because tumors acquire the ability to synthesize their own supply of testosterone and/or 5α-dihydrotestosterone (DHT) from nongonadal sources, particularly adrenal precursors, promoting signaling by the androgen receptor and enabling tumor progression and metastasis.

In a landmark 2013 study published in *Cell*, Dr. Sharifi identified the first example of a gene mutation present in human metastatic castration-resistant prostate cancer (mCRPC) tumors that increases the conversion of precursor steroids to DHT, permitting tumors to resume growth in the absence of gonadal testosterone.

Understanding Abi's Conversion

Abi, approved by the Food and Drug Administration in 2011 and administered orally as abi acetate, blocks tumoral androgen synthesis by inhibiting the essential catalytic enzyme cytochrome P45017A1 (CYP17A1), thereby prolonging mCRPC patients' survival. Ultimately, however, disease progression recommences and patients succumb.

In a 2015 *Nature* study exploring abi metabolism in prostate cancer patients, Dr. Sharifi and colleagues determined that abi is converted by the enzyme 3β-hydroxysteroid dehydrogenase (3 βHSD) to the more active Δ4-abiraterone (D4A). D4A, the researchers found, has more potent antitumor activity than its parent drug, blocking multiple steroidogenic enzymes and antagonizing the androgen receptor.

The latest *Nature* study by Dr. Sharifi's group delved deeper into abi metabolism, showing that D4A is converted into at least six downstream metabolites (three by 5α-reductase and three by 5β-reductase) in prostate cancer cells, mice and human CRPC patients.

One of those metabolites, 3-keto-5α-abiraterone (5α-abi), is present at higher concentrations than its precursor, D4A, in prostate cancer patients who take abi acetate, and is an androgen receptor agonist that promotes tumor progression. The researchers found that treating CRPC xenograft-bearing mice with 5α-abi significantly shortened their progression-free survival ($P < 0.01$). Prostate cancer cells treated with abi developed the ability to enhance the breakdown of tumor-inhibiting D4A to tumor-promoting 5α-abi by upregulating the endogenous conversion enzyme steroid-5α-reductase (SRD5A).

In essence, Dr. Sharifi discovered that advanced prostate tumors co-opt abi metabolism to increase androgen synthesis while accelerating elimination of the antitumor metabolite D4A.

Altering Metabolic Outcomes

Could the researchers improve abi's efficacy by altering its metabolism to promote accumulation of "good" D4A and block its reduction to "bad" 5α-abi?

Dutasteride is a drug that inhibits SRD5A, the D4A-reducing enzyme. In a phase 2 clinical trial, Dr. Sharifi and colleagues tested the effect of adding dutasteride to the abi acetate treatment regimen in men with mCRPC.

Analysis of blood samples from 16 patients showed an 89 percent decrease in mean concentration of 5α-abi after addition of dutasteride, and a near-doubling in mean serum concentration of D4A. Dutasteride did not affect the amount of the three 5β-reduced abi metabolites, suggesting that it biochemically targets 5α abi metabolism with remarkable specificity.

Fine-tuning abi metabolism in this way should intensify the drug's therapeutic benefit in mCRPC patients, though confirmatory randomized trials are needed. Manipulating the metabolic process to inhibit 5β-reductase might further elevate D4A and abi concentrations, producing additional therapeutic gains. Together, these findings shed light on a completely unanticipated aspect of abiraterone therapy and possible new directions for improving outcomes for patients with prostate cancer.

Androgen-Enhancing Gene Mutation Reduces Prostate Cancer Survival

Prostate cancer patients with an inherited gene variant that enhances androgen synthesis are highly likely to develop tumors with more rapid resistance to androgen deprivation therapy (ADT) and have faster cancer progression and

significantly reduced survival, a Cleveland Clinic/Mayo Clinic study determined.

The results suggest that the variant of the *HSD3B1* steroidogenic enzyme gene could be a powerful new biomarker capable of identifying patients with aggressive disease who warrant early escalated therapy, says Dr. Sharifi, the study's principal investigator.

The findings also could guide future treatment strategies for patients with the variant allele. "Overall, these data suggest that there may be a genetically defined subgroup of patients with prostate cancer who might benefit from upfront treatment with a next-generation anti-androgen along with standard medical or surgical castration," Dr. Sharifi says.

A clinical trial is underway at Cleveland Clinic to test alternate treatments in prostate cancer patients with the inherited *HSD3B1* mutation.

Dr. Sharifi's previous research had mechanistically linked the *HSD3B1* somatic mutation present in prostate cancer cell lines to castration resistance, but this study is the first to confirm that patients who possess the inherited germline variation actually fare worse clinically than those without it.

Probing the Mechanics of CRPC

For more than 70 years, androgen-deprivation therapy (ADT) has been the gold standard for systemic treatment of prostate cancer. Prostate cancer cells' growth depends on androgen stimulation of the cells' androgen receptor (AR), which drives expression of AR-induced oncogenes. With gonadal suppression, ADT dramatically reduces serum testosterone level, resulting in AR deactivation and inhibition of tumor growth.

After one to two years, however, most patients evolve from castration-sensitive to castration-resistant prostate cancer (CRPC), as a result of tumors' acquisition of androgen synthesis capability.

HSD3B1 encodes the enzyme 3β-hydroxysteroid dehydrogenase-1 (3βHSD1). 3βHSD1 catalyzes the initial, rate-limiting step in the conversion of adrenal precursors to DHT and is necessary for all pathways of DHT synthesis.

Dr. Sharifi found that a single nucleotide polymorphism of *HSD3B1* at position 1245, converting A to C, causes a gain of function in 3βHSD1, enabling the enzyme to resist proteasomal degradation. The resulting enzymatic accumulation increases androgen synthesis, enhances AR activation and accelerates tumor proliferation.

The *HSD3B1*(1245C) allele can be acquired either by somatic mutation in CRPC tumors (probably due to selection pressure from ADT) or by loss of heterozygosity of the wild-type allele in patients with germline heterozygous inheritance. While Dr. Sharifi's previous research had demonstrated the selection and expression of the mutant enzyme in a mouse xenograft model of CRPC tumors, the clinical relevance of inheritance of the variant allele in prostate cancer had not been examined in a large, representative cohort.

The latest study set out to retrospectively evaluate ADT resistance, disease progression and survival in prostate cancer patients who had inherited the variant *HSD3B1*(1245C) allele.

HSD3B1 Variant Relatively Common

The primary cohort consisted of prostate cancer patients who underwent prostatectomy at Cleveland Clinic prior to 2010 and who were treated with ADT for biochemical failure. Two validation cohorts at Mayo Clinic consisted of men who had undergone ADT for biochemical and/or nonmetastatic clinical failure after prostatectomy, and men with metastatic prostate cancer treated with ADT.

Germline DNA from each patient (either prostatectomy specimens or peripheral blood mononuclear cells) was obtained and genotyped for the variant *HSD3B1*(1245C) sequence. A total of 443 men were genotyped at the targeted locus, and their outcomes were analyzed using clinical data for progression-free survival, distant-metastasis-free survival and overall survival.

Frequency of the variant *HSD3B1*(1245C) allele in the pooled cohort was 29 percent, indicating that the polymorphism is relatively common.

Number of Variant Alleles Affects Survival

The researchers found that inheritance of the variant *HSD3B1*(1245C) allele strongly correlated with reduced survival (progression-free, distant-metastasis-free and overall).

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They also found that the number of variant alleles patients inherited was a major factor in their survival. Among heterozygotes in the primary study cohort, median progression-free survival from ADT initiation was 4.1 years compared with 2.5 years for homozygous variant men. Median distant metastasis-free survival was 6.8 years and 3.6 years, respectively. Thirty-five percent of heterozygote patients were alive at 10 years post-ADT initiation, while none of the homozygous variant men lived to that point. This correlation suggests that the extra copy of the polymorphism leads to increased intratumoral androgen synthesis.

Implications for Treatment, Surveillance

The results indicate that the presence of inherited *HSD3B1*(1245C) is a strong predictor of which patients will develop resistance to ADT. It could help guide decisions about whether early escalated treatment is warranted and what type of treatment may have the best chance of success.

"A simple blood test could allow us to personalize therapy by telling us which patients need to be treated more aggressively, such as with more intensive hormonal therapy," says Dr. Sharifi. "On the contrary, patients with metastatic cancer who do not carry the polymorphism may fare as well with ADT alone."

The researchers speculate that prostate cancer patients with the *HSD3B1*(1245C) genotype might be insufficiently treated with ADT alone and would benefit from further androgen axis inhibition with drugs such as enzalutamide or abiraterone acetate or chemohormonal therapy. The clinical trial at Cleveland Clinic will test whether sustained androgen signaling conferred by inheritance of the *HSD3B1*(1245C) genotype is reversible with a potent AR antagonist.

Furthermore, an *HSD3B1*(1245C)-based blood test could help inform active surveillance (AS) selection; men with the inherited genotype may be higher-risk AS candidates since they are unlikely to respond to ADT if the opportunity to cure localized cancer is missed.

More Prostate Cancer Research in Brief

Gene Expression Patterns in Normal Tissue Near Prostate Tumor Can Predict Clinical Outcome

Development of biomarkers that can accurately predict the biologic potential of early-stage prostate cancer has been challenging because of the heterogeneity in grade and multifocality of most tumors and the variable mixture of malignant and benign cells in the sampled tissue.

One approach to these challenges is to incorporate a deeper understanding of the biology of the nonmalignant stromal and epithelial cells present within and adjacent to the tumor, which may represent a generalized field effect related to tumor aggressiveness.

Field cancerization is exemplified by a range of genetic and epigenetic abnormalities that can be detected in normal-appearing tissues adjacent to cancers, including gene silencing by methylation, deletions in mitochondrial DNA, mutations in cancer-related genes and aberrant gene expression. Evidence for a field effect has been reported in a variety of cancer types, including head and neck, lung, colon, breast, stomach and bladder.

By analyzing gene expression in histologically normal-appearing tissue adjacent to prostate tumors in radical prostatectomy specimens, Cleveland Clinic researchers found evidence supporting the existence of a biologically meaningful field cancerization in prostate cancer. These gene expression patterns in normal tissue adjacent to cancer can predict clinical outcome, and thus may help identify patients with aggressive disease.

Furthermore, the Glickman Urological & Kidney Institute researchers determined that a 17-gene expression assay, the Genomic Prostate Score (GPS, owned and marketed as Oncotype Dx for Prostate Cancer by Genomic Health Inc.) — which previously had been validated to predict aggressive prostate cancer when measured in tumor tissue — was also associated with clinical outcome when measured in normal tissue, although the strength of association was weaker than in tumor.

For more details, see clevelandclinic.org/CancerFieldEffect.

Study Links Early Salvage Radiotherapy at Low PSA After Prostatectomy with Improved Survival

In the largest study of its kind, Cleveland Clinic researchers have found that prostate cancer patients who undergo early salvage radiotherapy (SRT) after radical prostatectomy, when prostate-specific antigen (PSA) levels are low, have significantly lower mortality than patients who are treated with delayed SRT at higher PSA levels.

The retrospective analysis of 2,454 node-negative patients with detectable post-prostatectomy PSA levels determined that SRT initiated at PSA levels ≤ 0.2 ng/mL was associated with reduced rates of both prostate cancer-specific mortality and all-cause mortality, compared with SRT at higher PSA levels.

"Mortality outcomes from salvage radiotherapy after prostatectomy have been largely unexplored, so this study provides us with important information," says senior author Rahul D. Tendulkar, MD, Clinical Director of the Department of Radiation Oncology at Cleveland Clinic Cancer Center.

The analysis included patients followed for a median of 5.1 years after SRT with or without neoadjuvant or concurrent ADT. Findings were presented at the 2016 annual meeting of the American Society for Radiation Oncology (ASTRO) in Boston.

"The PSA at time of salvage radiotherapy seems to be an independent predictor of mortality outcomes," Dr. Tendulkar says. "In previous studies, most predictors of mortality have been tumor-related. But in our study, PSA was a significant predictor of mortality, while some tumor-related factors such as extraprostatic extension and surgical margins were not significant in mortality outcomes upon multivariate analysis."

These findings are supportive of current American Society for Radiation Oncology and American Urological Association consensus guidelines, which recommend that SRT should be offered at the first sign of a PSA rise after prostatectomy.

Optimal postoperative management of men with prostate cancer remains an area of ongoing research. The present study does not support basing treatment decisions solely on detectable PSA; instead, a combination of factors should be considered, Dr. Tendulkar says.

"There is no magic PSA cut point before which radiation therapy should be initiated," he says. "It still requires clinical judgment to determine the best course of treatment for each patient. We have to take into account how well the patient has healed after prostatectomy, the rate of rise of PSA, comorbidities and life expectancy. Personalized care is very important to select the right patient for the right treatment."

For more details, see clevelandclinic.org/TendulkarSRT.

Newly Identified Pathway Helps Cancer Cells Survive DNA Damage

Cleveland Clinic researchers have discovered a novel biochemical pathway that enables prostate cancer cells to survive extensive DNA damage that normally would trigger cell death.

In normal cells, poly-ADP-ribose polymerase-1 (PARP-1) modulates DNA repair and cellular survival by recognizing DNA strand breaks, binding to the DNA, inducing a conformational change and synthesizing poly-ADP ribose (PAR), the essential first step in DNA repair.

Excessive DNA damage in a normal cell leads to PARP-1 overactivation, and oversynthesis of PAR, which kills the cell — a process called parthanatos.

In cancer cells, heightened concentrations of reactive oxygen species lead to DNA damage and ultimately upregulation of oligoadenylate synthetase enzymes (OASs), which greatly reduce PAR production. Decreased PAR synthesis enables cancer cells to escape parthanatos and survive an otherwise lethal amount of DNA damage.

Inhibiting OAS synthesis could increase PAR production and sensitize many cancer cells to DNA damage while sparing normal cells.

Identifying the pathway "is fundamentally interesting biochemistry, and also presents a clear opportunity to investigate a novel way to inhibit the ability of cancer cells to deal with excessive DNA damage, whether endogenous or exogenous," said George Stark, PhD, of Cleveland Clinic Lerner Research Institute's Department of Cancer Biology, who with colleague Robert Silverman, PhD, made the discovery.

George Stark, PhD

Robert Silverman, PhD

The scientists, along with their collaborators at Cleveland Clinic, the University of Chicago and Thomas Jefferson University, are seeking funding for translational research. Although they are focusing on prostate cancer, their approach has broader implications. "If we prove the principle in prostate cancer and develop effective OAS inhibitors, I think there would be significant interest in translating this for other cancers," Dr. Stark says.

For more details, see clevelandclinic.org/DNADamageSurvival.

IsoPSA Improves Detection of Clinically Important Cancers

The prostate-specific antigen test has relatively poor specificity for prostate cancer and cannot differentiate indolent from aggressive disease. Newer biomarker tests have only modestly improved diagnostic accuracy.

The clinical utility of these tests will always be limited because biomarker concentrations may be affected by cancer-unrelated physiological processes, as well as the relative lack of specificity of these biomarkers to the cancer phenotype. Further, the histologic heterogeneity of prostate cancer will generally limit the sensitivity of tests that analyze only one or several unique biomarkers to the exclusion of others that may indicate the presence of disease.

Cleveland Clinic, in collaboration with colleagues at Cleveland Diagnostics Inc., and in clinical research centers across the country, has taken an "outside the box" approach to the development of novel diagnostic tests for cancer and other diseases, based on the identification of molecular structural changes in protein biomarkers as opposed to their concentration in serum or other body fluids.

The researchers have developed the IsoPSA™ test, which identifies molecular structural changes in the PSA protein biomarker as opposed to PSA concentration. IsoPSA interrogates the entire PSA isoform distribution in a single assay to yield a unique ratiometric parameter.

Interim clinical data from an ongoing multicenter prospective trial to assess the diagnostic performance of IsoPSA, reported at the American Urological Association's 2016 annual meeting, show that the test can reliably discriminate structural changes in the PSA protein, which then correlates with the presence or absence of cancer.

By adding standard clinical information in a multivariate analysis, the IsoPSA test has also been shown in this prospective trial to have the potential to differentiate patients at risk for high-grade disease.

For more details, see clevelandclinic.org/IsoPSA

Study Shows **Active Surveillance** Is Safe and Viable in Some Metastatic Renal Cell Carcinoma Patients

Certain carefully selected metastatic renal cell carcinoma (mRCC) patients who choose close monitoring rather than immediate systemic therapy can live for months or several years before cancer progression while avoiding the significant burdens of treatment, a Cleveland Clinic-led study has found.

KEY POINTS

Active surveillance (AS) is often employed in cases of localized renal cell carcinoma but infrequently in patients with advanced/metastatic disease.

While AS would seem to offer clinical and quality-of-life benefits for patients with slow-growing metastases, prospective assessment was lacking.

A single-arm, multicenter study tracked metastatic renal cell carcinoma patients on AS and confirmed its viability.

Carefully selected AS patients can survive as long as several years before progression while avoiding treatment burdens, and without compromising eventual therapy or worsening their emotional status.

Dr. Rini is Director of Cleveland Clinic Cancer Center's Genitourinary Cancer Program and Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

He can be reached at rinib2@ccf.org or 216.444.9567.

Active surveillance, when properly applied, doesn't appear to compromise response to eventual systemic therapy, reduce overall survival or worsen patients' emotional state during the waiting period, the researchers determined.

More research is needed to validate the results and to explore the risks and benefits of surveillance as more novel therapies become available, says the study's principal investigator, Brian Rini, MD, FACP, Director of Cleveland Clinic Cancer Center's Genitourinary Cancer Program. But the phase 2 study indicates that delayed treatment with close monitoring is a safe, viable approach for some mRCC patients with limited metastatic disease and limited risk factors, and provides guidance for clinicians applying the strategy.

"There is a public perception that all cancers should be treated immediately because they are equally lethal," Dr. Rini says. "But what we've seen in this small clinical trial is that a subset of adults with advanced kidney cancer have slow-growing disease that can be safely managed using active surveillance. That could spare those patients the inconvenience and potentially debilitating side effects of aggressive treatments for about a year, and in some cases several years, without worsening anxiety and depression."

Prospective Data Lacking

mRCC can have a highly variable course. Previous research involving patients who received immediate therapy showed that favorable-risk patients with zero pretreatment clinical features associated with reduced survival had a median survival time of 20 months, while poor-risk patients with three or more adverse risk factors had a median survival time of four months.

Although systemic treatment employing tyrosine kinase inhibitors of the vascular endothelial growth factor can extend survival in mRCC patients and is the standard of care, this approach is palliative, not curative, and requires chronic therapy, with significant toxicity and morbidity and entailing considerable time commitment and expense for patients.

Active surveillance is a clinical tactic sometimes employed with localized RCC but infrequently in patients with advanced/metastatic disease. Intuitively, active surveillance as an initial strategy would seem to offer clinical and quality-of-life benefits for mRCC patients who show indolent growth of metastases. Several small retrospective reports and a randomized discontinuation trial involving deferred treatment in mRCC patients have suggested that delays do not have an adverse impact. However, prospective assessment of active surveillance in mRCC had not been undertaken prior to this study.

Methodology and Assessment

Between 2008 and 2013, Dr. Rini and colleagues at five medical centers in the United States, Spain and the United Kingdom enrolled 52 treatment-naïve mRCC patients. Four were excluded from the analysis, leaving a cohort of 48. Participants' decisions to take part and thus choose active surveillance over immediate systemic treatment were made jointly with their treating physicians, as were decisions to discontinue observation and initiate systemic therapy.

Study participants underwent baseline and regular repeat CT scans and clinical assessments to determine change in tumor burden and time to progression. They also were periodically assessed for quality of life, anxiety and depression status changes. Overall survival, progression-free survival and best overall response after therapy (the latter for those participants who discontinued active surveillance and initiated treatment) were recorded.

Progression and Survival Outcomes

Participants were followed for a median of 38.1 months. Thirty-seven discontinued surveillance and began systemic therapy after progression while six continued on surveillance. The median time on surveillance was 14.9 months.

In the 42 patients who did not undergo tumor resection while on surveillance, the median change in tumor burden over the surveillance period was 1.3 cm, with a median growth rate of 0.09 cm per month.

Twenty-two (46 percent) of the 48 study participants died, all from mRCC. Estimated median overall survival from the start of surveillance was 44.5 months.

Of the 31 patients who discontinued surveillance and for whom subsequent systemic therapy data were available, 10 (32 percent) had objective partial responses. Median overall survival was 38.6 months. Progression-free survival was not assessed.

Patients' anxiety, depression and quality-of-life questionnaire scores during the course of surveillance did not change significantly compared with baseline, indicating that delaying treatment did not have a negative impact on their emotional status.

The study was a single-arm design, so it is not possible to directly compare outcomes of surveillance patients with those of a concurrent group who received immediate systemic therapy. However, the surveillance patients' median survival rates and objective response rates to subsequent treatment are indicators that it is a safe, viable approach, Dr. Rini says.

"Median survival in metastatic kidney cancer in recent trials has been about 30 months," he says. "Our active surveillance patients' estimated median survival was 44.5 months. Much of that is attributable to patient selection — patients had to have slow-growing disease to qualify for the observational approach in the trial. But it didn't appear that surveillance compromised survival. Similarly, when we looked at response to subsequent therapy, it looked the same or better than in historical controls. It's not a perfect comparison, but it suggests that these active surveillance patients do just as well when you start them on treatment."

Selection Criteria for Surveillance

The researchers' analysis of baseline clinical characteristics showed that 29 patients with one or no International Metastatic Database Consortium (IMDC) adverse risk factors and two or fewer organs with metastatic disease had an estimated

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median surveillance time of 22.2 months, while all other patients with more IMDC adverse risk factors and multiple metastases sites had an estimated median surveillance time of 8.4 months.

Clinicians can use those clinical characteristics in a prognostic manner to identify patients for whom active surveillance may be a successful strategy. Two patients under surveillance in the study developed new central nervous system (CNS) metastases, highlighting the importance of routine CNS imaging during the observation period.

"Active surveillance is not going to be the appropriate approach for every patient with metastatic renal cell carcinoma," Dr. Rini says. "From years of seeing the disease, I would estimate that it's one or two patients out of 10 who could be watched. It wasn't completely unheard of for a physician to recommend delayed treatment, but it was based on experience and a bit of gut instinct. It had never to our knowledge been studied prospectively. I think that's the value our trial added — examining the selection criteria and more precisely defining the outcome of the surveillance approach."

Frederic Reu, MD

NEWS & INSIGHT

Smarter Drug Discovery Yields Promising Results in Multiple Myeloma Therapy

An innovative screening assay developed by a Cleveland Clinic-led team of researchers has helped identify CCF642 — a small-molecule compound that has led to a patent for a new class of anticancer agents.

CCF642 has broad anti-myeloma activity in vivo, prolonging survival in a mouse model of multiple myeloma comparable to the survival extension achieved by the FDA-approved first-line therapeutic agent bortezomib. CCF642 appears to work at least in part by inhibiting protein disulfide-isomerase (PDI), the bottleneck enzyme that regulates protein folding prior to secretion, which is a highly myeloma-relevant process. Multiple myeloma cells secrete massive amounts of proteins, so disruption of the protein-folding process through PDI inhibition should increase cellular stress and trigger apoptosis, potentially augmenting existing therapies. The researchers detailed their findings in the journal *Cancer Research*. A patent for an analog of CCF642 and its derivatives was issued in June.

"Our study aimed to identify a novel mechanism to treat myeloma and avoid unnecessary animal experiments by simulating key aspects of an organism in the laboratory," says Frederic Reu, MD, an oncologist in Cleveland Clinic Cancer Center's Department of Translational Hematology and Oncology Research. "The drug we identified, CCF642, really does seem to work through a novel mechanism, and it is effective across the board for myeloma cells and in an animal model of myeloma. So, in general the screen seems to be effective, and its first lead compound appears promising."

Drug Discovery Tailored to Myeloma

The assay screened candidate compounds by simulating variables such as renal clearance and hepatic metabolism, along with aspects of the myeloma microenvironment, normal bone marrow cell tolerability and activity against different multiple myeloma cell lines.

"We only pursued molecules that worked in a panel of genetically heterogeneous myeloma cell lines," Dr. Reu says. "CCF642 fulfilled the mandate for activity across myeloma cell lines. It was tested in 10 different myeloma cell lines and killed them at similar drug concentrations."

After the potency of CCF642 was established, the researchers evaluated the agent in an aggressive syngeneic mouse model of multiple myeloma. It significantly prolonged the life of mice engrafted with myeloma and suppressed myeloma cell growth. In addition, it did not cause substantial bone marrow toxicity.

Survival prolongation in the CCF642-treated mice was statistically equivalent to extensions achieved in the same mice strain by the maximum tolerated dose of bortezomib, the most potent FDA-approved upfront myeloma drug. Looking to the future, Dr. Reu notes that an agent such as CCF642 might prove useful for patients with bortezomib resistance because its mechanism of action is different than that of the proteasome inhibitor.

Dr. Reu's team is using crystallography to identify the exact interaction of CCF642 with PDI, and validating PDI as a target using llama-derived intrabodies.

For a more detailed version of this article, see clevelandclinic.org/MyelomaModelDrug.

Vamsi Velcheti, MD

Clinical Trial Based on Cleveland Clinic Research Will Test Enhanced Immunotherapy in Lung Cancer

Building on their extensive research in enhancing immunotherapy's effectiveness in lung cancer, Cleveland Clinic Cancer Center scientists are launching a phase 2 clinical trial to test a promising drug combination that may improve the anti-tumor activity of nivolumab.

The recent advent of immune checkpoint inhibitors such as nivolumab has been a breakthrough for seemingly intractable advanced and metastatic cancers, significantly improving survival.

Unfortunately, objective response rates to immune checkpoint inhibitors are very low — nivolumab's is only about 20 percent as second-line therapy for non-small cell lung cancer (NSCLC) — meaning that the majority of patients are not benefiting from this approach.

A key factor in this limited response is tumors' ability, via the epigenetic protein DNA methyltransferase 1(*DNMT1*), to suppress neo-antigen expression that would otherwise prime the immune system. This enables cancer cells to avoid immune recognition.

"If you don't have an endogenous immune response to begin with, then prescribing drugs that break the tumor's immunosuppressive capabilities won't make any difference," says Cleveland Clinic Cancer Center researcher Vamsi Velcheti, MD. "Tumors become invisible to the immune system."

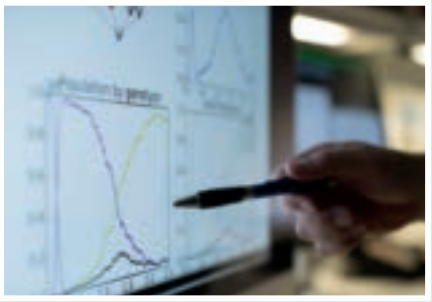
Drugs such as decitabine can inhibit epigenetic suppression by depleting *DNMT1*. They have the added advantage of being able to directly cytoreduce NSCLC and other cancers by inducing differentiation, which renders cancer cells nonproliferative. This mechanism is relatively nontoxic compared with other chemotherapeutic approaches for NSCLC.

But in solid tissue, enzymatic activity via cytidine deaminase (CDA) degrades decitabine in a matter of minutes, rendering it useless.

Dr. Velcheti and his collaborator, Cleveland Clinic Cancer Center researcher Yogen Saunthararajah, MD, have investigated pharmacological regimens that can optimize the pharmacology of decitabine. They recognized that the depletion of decitabine was undermining its potential as an effective epigenetic drug to induce immune priming in solid tumors. In a phase 1 clinical trial, they showed that pairing decitabine with tetrahydrouridine, a drug that blocks the decitabine-degrading enzyme CDA, solves the bioavailability problem.

Drs. Velcheti and Saunthararajah will conduct the randomized phase 2 trial to determine whether the nivolumab/decitabine/tetrahydrouridine combination as second-line therapy improves objective response, progression-free survival and overall survival in NSCLC patients compared with nivolumab alone. The trial, which aims to enroll approximately 60 patients at sites in Cleveland, Bethesda, Md., and Weston, Fla., begins in February 2017.

"Using noncytotoxic epigenetic therapy, we are taking a very different approach," says Dr. Velcheti, the trial's principal investigator. "We are leveraging the potential of the combination therapy to induce differentiation in the tumor, unmask its cancer-specific antigens and enable immune priming, promote an immune response, and extend the bioavailability of decitabine, all of which should boost nivolumab's effectiveness."



Mathematical Oncologist Jacob Scott, MD, Is Writing New Equations to Decipher Cancer

Targeted therapies work remarkably well on cancer cells — until they suddenly don't. Drug resistance has become the norm, almost expected, for these promising treatments.

Why Does It Happen? And How Can It Be Prevented?

Solving the mysteries of acquired resistance may require more than in vivo, in vitro and in silico research. It may take something more foundational, like discovering a "Newton's law of biology," says Jacob Scott, MD.

The newest member of Cleveland Clinic Cancer Center's Department of Translational Hematology and Oncology Research is one of

(continued on page 10)

Jacob Scott, MD

a small number of people positioned to help identify it.

Physics + Oncology + Math

Dr. Scott graduated from the U.S. Naval Academy with a degree in physics and served aboard the ballistic missile submarine USS Louisiana as a nuclear engineer. After leaving the Navy in 2002, he embarked on a medical career, repurposing his physics acumen in radiation oncology.

As a resident physician at Moffitt Cancer Center in Tampa, Florida, he attended a lecture by mathematician Alexander R.A. Anderson, PhD, that introduced him to the nascent field of mathematical oncology. This emerging discipline uses the tools of mathematics to characterize and predict tumor growth and the development of drug resistance.

"It combined the theoretical thinking of physics with the biology of cancer," says Dr. Scott. "I never knew those fields could be connected."

Dr. Scott soon joined Moffitt's Integrated Mathematical Oncology Department and worked alongside Dr. Anderson, physicists, computer scientists and other nonbiological thinkers to uncover fundamental principles of tumor growth. During his time at Moffitt, he began a math program at the University of Oxford, where he soon will complete a doctorate in mathematical biology.

In August 2016, Dr. Scott joined Cleveland Clinic with plans to build his own mathematical oncology research program. He continues to care for sarcoma patients as well, making him perhaps the nation's only mathematical oncology researcher who is also a clinical oncologist.

Why Cancer Needs Math

A decade ago, mathematical oncology didn't exist. The field has evolved with technology.

"Today, we can measure the cancer genome with more precision than ever before, but we don't yet have theories to understand what we're measuring," says Dr. Scott. "We need theory to catch up to technology."

That's where mathematical analysis comes in. Equations, algorithms and modeling can help make sense of large amounts of data, not just statically but dynamically — why certain factors increase or decrease over time, and how factors are interrelated.

Researchers in theoretical ecology, population genetics and genomics also use computational methods to study cancer. But mathematical oncologists use them for a different purpose: to identify basic, essential principles that govern cancer biology. Mathematical models of these laws can help predict behavior of cancer cells and thereby suggest more effective treatments.

"As medicine advances, part of our challenge is dealing with enormous amounts of information — examining giant data sets, such as genomic data, and being able to analyze and extract things that will have clinical benefit," says Brian Bolwell, MD, FACP, Chairman of Cleveland Clinic Taussig Cancer Institute. "Mathematical oncology applies that analytical approach to cancer, and Dr. Scott brings a lot of creativity to this exciting new field."

Recent Findings

Before joining Cleveland Clinic, Dr. Scott focused on developing mathematical models of cancer metastases. Currently, his attention is on the evolution of drug resistance.

"By understanding the evolution better, I hypothesize that I can perturb the process or find contingencies," he says.

In a recent study, he and his colleagues developed a mathematical model of an evolving bacterial population that predicted the likelihood of resistant strains emerging. The researchers used the model to show how prescribing a specific sequence of antibiotics can steer bacterial evolution to prevent resistance. Another study used mathematical modeling to identify strategies to potentially re-establish sensitivity in non-small cell lung cancer cells that had become resistant to first-line ALK inhibitors.

Developing additional mathematical models of drug resistance will be central to Dr. Scott's work at Cleveland Clinic.

"I've been studying how a drug shapes a tumor genetically, not just how many cells it kills," he says. "I suspect there are drugs deemed 'ineffective' that we can resume using in new ways, maybe to prime tumors to react better to other drugs or to make it more difficult for tumors to evolve."

As more mathematicians go to work in cancer labs and clinics, progress will accelerate, he concludes.

VeloSano Raises More Than $3 Million for Cleveland Clinic Cancer Research

This past July, nearly 1,600 cyclists from 24 states and two countries rode in VeloSano 3, pedaling more than 81,000 miles and raising $3.37 million to support cancer research at Cleveland Clinic.

"The participation of VeloSano riders and volunteers in this annual event furthers our ability to provide the best patient care and work toward our ultimate goal of beating cancer," says Brian J. Bolwell, MD, Chairman of Cleveland Clinic's Taussig Cancer Institute. "Funds raised through VeloSano bring sophisticated cancer research to our patients. In 2015 alone, 3,261 patients participated in more than 440 cancer-related clinical trials conducted at Cleveland Clinic, thanks in part to VeloSano."

Help from Our Friends

VeloSano has gained significant momentum in raising money for cancer research at Cleveland Clinic due to the support of its partners, including the Donna and Stewart Kohl Fund, the Cleveland Indians and law firm Jones Day, which have each pledged to support the event for several years to come. Earlier this year, the Donna and Stewart Kohl Fund pledged $1 million to support VeloSano over the next four years.

With VeloSano's support from more than 1,000 volunteers and 60 event partners, every dollar raised by riders and virtual riders directly benefits cancer research at Cleveland Clinic. Funds will be allocated across the Cleveland Clinic enterprise to support the research areas of cancer genomics, immunotherapy and clinical trials.

"This year, more than 21,000 donations were received from all 50 states, Washington, D.C., and 31 countries; more than 5,300 volunteer hours were logged; and nearly 82,000 miles were covered on bikes," says Stewart A. Kohl, VeloSano founder and co-CEO of The Riverside Company. "Most importantly, collectively we've raised more than $8 million over the past three years, and these dollars are being immediately distributed to research being performed right here in Northeast Ohio."

Looking Ahead

The research VeloSano 3 will support will be announced in early 2017.

VeloSano 4 weekend is scheduled for July 21-23, 2017, and will once again be chaired by Paul Dolan, Chairman and CEO of the Cleveland Indians, and John Saada, Partner at Jones Day. Registration is open now at velosano.org.

Cancer Advances provides information from Cleveland Clinic cancer specialists about innovative research and diagnostic and management techniques.

Please direct correspondence to:
Taussig Cancer Institute/R35
Cleveland Clinic
9500 Euclid Ave.
Cleveland, OH 44195

Cleveland Clinic Cancer Center annually serves thousands of cancer patients. More than 450 clinicians, scientists and other cancer specialists are committed to researching and applying the latest, most effective techniques for diagnosis and treatment to achieve long-term survival and improved quality of life for all cancer patients. Cleveland Clinic Cancer Center is part of Cleveland Clinic, an independent, nonprofit, multispecialty academic medical center.

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John Mangels

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Amy Buskey-Wood

Photography
Russell Lee, Tom Merce, Steve Travarca, Greg Mueller

Medical Illustration
Joe Kanasz

Chemotherapy After Radiation **Extends Survival** in Unfavorable-Risk Low-Grade Glioma

Dr. Suh is Chairman of Cleveland Clinic Cancer Center's Department of Radiation Oncology, a staff member of the Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, and Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

He can be reached at suhj@ccf.org or 216.444.5574.

On Twitter: @DrJohnSuh

Patients with grade 2 gliomas treated with a chemotherapy regimen of procarbazine, lomustine (CCNU) and vincristine (PCV) after radiation therapy (RT) lived significantly longer and had significantly slower disease progression than patients treated with RT alone, according to results of a multicenter study that included Cleveland Clinic.

While the survival benefits of RT+PCV treatment are substantial, the combination therapy's toxicities are greater than with RT alone. That means patients and their physicians will need to consider whether the potential survival gains warrant additional toxic effects.

"Perhaps the most encouraging result is the number of long-term survivors with unfavorable-risk, low-grade glioma," or LGG, reports John Suh, MD, Chairman of Cleveland Clinic Cancer Center's Department of Radiation Oncology and a co-author of the study published in the *New England Journal of Medicine*. "This is the first trial to demonstrate a significant survival benefit for high-risk LGG patients treated with combined modality therapy.

"However, the hematologic toxicities of RT+PCV are greater and the logistics of delivering PCV can be complex," Dr. Suh says. "Temozolomide has been used frequently in the past decade, given its oral administration, better tolerance and its establishment as standard therapy for glioblastoma. Unfortunately, no prospective trials have compared temozolomide to PCV in LGG patients. Physicians and patients will need to determine the value of a more toxic regimen in which a survival benefit has been clearly demonstrated compared to one that has been extrapolated without level 1 evidence."

KEY POINTS

Low-grade gliomas (LGGs) can have a long natural history, and treatment goals are to extend progression-free survival and maintain patients' quality of life.

Various chemotherapy regimens cause tumor regression in patients with recurrent LGGs, but the timing of postoperative radiation therapy (RT) is controversial, and treatment decisions must also involve the decision to add chemotherapy.

A multicenter prospective randomized trial evaluated a regimen of procarbazine, lomustine and vincristine (PCV) with and without RT in unfavorable-risk LGG patients.

Long-term results show the RT+PCV combination significantly extended survival and slowed disease progression compared with RT alone.

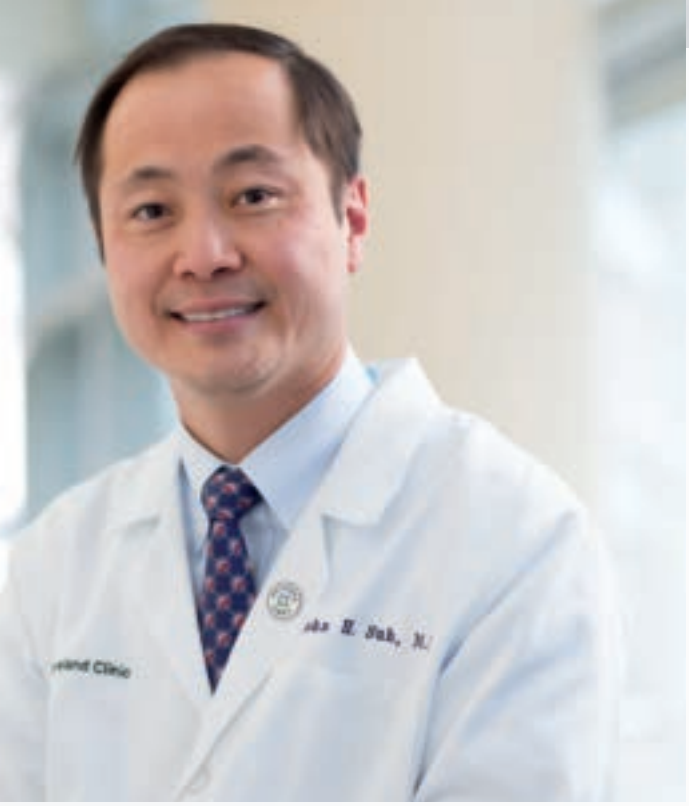
Clinicians must weigh whether the demonstrated survival benefits but greater side effects of RT+PCV justify its routine use versus temozolomide, the standard of care in grade 3 and 4 gliomas, which has better tolerability but only an extrapolated survival benefit.

LGG's Variable Course

LGGs, which constitute between 5 and 10 percent of all adult primary brain tumors, are a heterogeneous group of tumors with a variable and potentially long course. They typically affect young patients. Progression occurs in nearly all patients, and nearly all die prematurely. Treatment is a balancing act — administering therapy to extend progression-free and overall survival while maintaining quality of life by minimizing treatment-related morbidity, including seizures, cognitive decline and neurologic deficits.

In general, LGG treatment paradigms have involved immediate surgery and RT, or upfront surgery alone with delayed RT until the time of tumor progression. Surgery typically is not curative, and the timing of postoperative RT is controversial, particularly when considering its acute and delayed side effects and their impact on patients' quality of life.

Treatment decisions are guided by prognosis and must involve the timing of RT as well as the decision to add chemotherapy. Risk factors for poor prognosis include age > 40, tumors ≥ 6 cm, neurologic function score > 1, tumors crossing midline and astrocytoma-dominant histology. More recently, tumor molecular markers including elevated proliferative index, absence of a 1p19q codeletion and absence of mutations in the *IDH1/2*



genes have also been determined to predict poor outcomes.

Previous studies had shown that various chemotherapy regimens caused tumor regression in patients with recurrent LGGs. In particular, two small nonrandomized trials demonstrated that the PCV combination given as initial therapy produced favorable response rates in a meaningful proportion of patients.

Those findings prompted an initiative to test the PCV regimen in a prospective, randomized trial comparing outcomes in unfavorable-risk LGG patients (defined as age ≥ 40 and/or subtotal resection of a supratentorial World Health Organization grade 2 glioma) who received RT with and without chemotherapy. Patients were accrued from 1998 to 2002.

Initial results of the RTOG 9802 protocol, published in 2012, showed that RT+PCV significantly improved progression-free survival (PFS) but not overall survival (OS). Between years 0 and 2 post-diagnosis, OS and PFS were similar for the RT-alone and RT+PCV cohorts; however, post hoc subset analysis showed that beyond two years, the RT+PCV combination provided an advantage in both PFS and OS, suggesting that chemotherapy produced a delayed benefit.

This study presents RTOG 9802's long-term results.

Treatment Details

Between 1998 and 2002, 251 patients with supratentorial grade 2 glioma received either RT alone or RT+PCV, with Cleveland Clinic being one of the lead enrollers for this study. Patients aged 18-39 were eligible if they underwent a subtotal resection or biopsy, while those aged 40 and older were included if they underwent a biopsy or resection of any of the tumor.

The dose of 54 Gy was delivered by external beam in 30 fractions of 1.8 Gy/fraction, five days a week over six weeks to a gross tumor volume defined by MRI plus a 2-cm margin. Chemotherapy was administered within a month of RT completion and consisted of six cycles of PCV repeated at eight-week intervals, in the following doses:

- **Procarbazine:** 60 mg/m^2 orally per day on days 8-21
- **CCNU:** 110 mg/m^2 orally on day 1
- **Vincristine:** 1.4 mg/m^2 intravenously on days 8 and 29

Patients underwent a Mini-Mental State Examination (MMSE) at baseline and a preoperative and postoperative MRI. Both MMSE and MRI were repeated during treatment and at protocol-specified points until tumor progression, with MMSE ending at five years.

Separation of the Survival Curves

In contrast to early results from RTOG 9802, the more mature analyses found the RT+PCV group had an approximate 5.5-year benefit in OS, with an additional 20 percent in long-term survivors.

With a median follow-up time of 11.9 years, survival outcomes were:

- **PFS:** 10.4 years for RT+PCV versus 4.0 years for RT alone
- **OS:** 13.3 years for RT+PCV versus 7.8 years for RT alone
- **5-year OS rate:** 72 percent for RT+PCV versus 63 percent for RT alone
- **10-year OS rate:** 60 percent for RT+PCV versus 40 percent for RT alone

(continued on page 14)

(CONTINUED)

Dr. Suh offers several thoughts on the late separation of the survival curves. "First and foremost, longer follow-up permits a greater number of events to occur, which increases the power to detect statistically significant differences," he says. "There is also the possibility that two-year survivors had favorable molecular features and more complete resections, allowing the maximal benefit of PCV to be realized.

"It should also be emphasized that the survival curves cross," Dr. Suh says. "Although there were no PCV-related deaths, it is possible that patients receiving PCV experience side effects that decrease their functional status, precluding salvage therapies that may prolong survival." Dr. Suh also notes that the trial was not stratified by molecular status at randomization because it began in 1998 — thus imbalanced molecular features may have influenced initial results.

Toxicity, Morbidity and Cognition

As expected, the frequency and severity of toxic effects were greater in the RT+PCV group. Most were grade 1 or 2, which is consistent with the effects of other multiagent regimens. Only four patients required transfusions, and no chemotherapy-induced malignancies or deaths attributable to either RT or PCV have occurred. Although late toxicities are a potential concern, no grade 3 or greater events have been reported in the RT+PCV cohort, compared with two in the RT-only arm.

An unexpected finding involved improved cognitive function among both study cohorts during the course of the trial. Twelve percent of patients in the RT+PCV group had increased cognitive function scores from baseline at five years, compared with 5 percent in the RT-only group. Although the MMSE is a relatively insensitive tool that may miss some cognitive changes, the apparent cognition benefits from more aggressive therapies probably reflect the lack of tumor progression, Dr. Suh says.

Treatment Decisions

Even with the encouraging survival findings in this long-term analysis, Dr. Suh says some physicians may still have reservations about administering the older PCV regimen based on its profile compared to temozolomide, the standard of care in grade 3 and 4 gliomas.

No prospective trials have analyzed temozolomide versus PCV for low-grade gliomas, although a trial for 1p/19q codeleted anaplastic gliomas was recently modified to include high-risk low grade gliomas, according to Dr. Suh. Therefore, physicians and patients must weigh the value of a more toxic regimen with a clearly demonstrated survival benefit versus one with better tolerability but only an extrapolated survival benefit, he says.

"Physicians will need to decide whether the higher side effects of RT+PCV justify its routine use or if temozolomide should be used, given its ease of administration and established use in malignant gliomas," he says.

Plans to conduct additional analyses for various molecular subsets are underway to better determine which patients will benefit most from PCV and to personalize treatment recommendations accordingly.

"As our understanding of the biology of low-grade glioma matures, future trials will become more targeted and patient-centric," Dr. Suh says. "For now, the results of this trial provide a strong foundation to improve OS, PFS and quality of life for high-risk, low-grade glioma patients."

More Brain Cancer Research in Brief

Immunotherapy and Glioblastoma: Assessing Strategies Across a Range of Trials

Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center is participating in clinical trials assessing a range of immunotherapeutic approaches for glioblastomas.

Vaccine-Based Approaches

Unlike some cancers, glioblastomas are not inherently immunogenic. Inducing immune responses is challenging.

One approach uses a peptide-based vaccine to induce an immune response. Survivin is an intracellular protein that regulates cell division and inhibits apoptosis. In cancers, high-level survivin expression is associated with poor outcomes, disease recurrence and therapy resistance. These observations prompted development of SurVaxM, a synthetic long peptide mimic vaccine that stimulates an immune response to survivin.

An ongoing phase 2 study combines SurVaxM with the oral chemotherapy agent temozolomide in patients with newly diagnosed glioblastoma. Cleveland Clinic and Roswell Park Cancer Institute are participating.

Additional vaccine-based immunotherapy approaches in trials here and at other centers include:

- **ICT-107**, an autologous vaccine that targets six antigens associated with glioblastoma, in phase 3 testing for newly diagnosed glioblastoma.
- **SL-701**, a glioma-associated antigen vaccine, in phase 2 testing for use in recurrent glioblastoma.

Immune Checkpoint Inhibitors

These agents target molecules/pathways that restrict immune responses, and can enable a patient's T cells to attack cancer cells by releasing the brakes on the immune system.

Two multicenter clinical trials at Cleveland Clinic are investigating the efficacy of a checkpoint inhibitor, the anti-PD-1 monoclonal antibody nivolumab, in newly diagnosed glioblastoma patients with either unmethylated O6-methylguanine-DNA-methyltransferase (MGMT) or methylated MGMT.

Oncolytic Viral Therapies

These work on the premise that a modified virus can infect tumors and cause them to self-destruct, facilitating an immune response against the cancer. Viruses being investigated in glioblastoma include poliovirus, genetically engineered poliovirus, the genetically engineered adenovirus DNX-2401, measles virus, the retroviral replicating vector Toca 511 and herpes simplex virus.

The furthest along in development is Toca 511, which expresses the cytosine deaminase gene and selectively delivers the gene to the tumor. It is being studied in combination with Toca FC, a novel formulation of the antifungal drug flucytosine that is converted to the anticancer drug 5-fluorouracil within infected cancer cells.

A phase 2/3 study of Toca 511 and Toca FC in subjects undergoing surgery for recurrent glioblastoma/anaplastic astrocytoma is underway at sites including Cleveland Clinic.

Targeting Myeloid-Derived Suppressor Cells

Myeloid-derived suppressor cells (MDSCs) accumulate in multiple tumor types and suppress cytotoxic immune cells via cytokine secretion. Cleveland Clinic investigators have shown that glioblastoma patients have elevated MDSCs in blood and tumor, and that these MDSCs produce reversible T-cell dysfunction.

The researchers developed an MDSC targeting strategy that relies on low dosing of 5-fluorouracil, a common chemotherapy. In preclinical models, this strategy severely attenuated MDSC numbers and glioblastoma growth while increasing cytotoxic T-cell numbers. A phase 1 trial at Cleveland Clinic is investigating a chemotherapeutic strategy targeting MDSC immunosuppression using the oral chemotherapeutic capecitabine plus the angiogenesis inhibitor bevacizumab in patients with recurrent glioblastoma.

For more details, see clevelandclinic.org/glioblastomatrials.

New Approach to Glioblastoma Aims to Turn Off Tumors' Molecular Motors

Despite recent therapeutic advances, survival rates of patients with glioblastoma and other brain malignancies remain low. Cleveland Clinic and other major centers are investigating new treatment strategies.

One of the most intriguing involves targeting the activity of molecular motors, which propel malignant glial cells through the brain's white matter and cortex. Intervening in or inhibiting the activity of these motors stops the cells from moving, opening a new area of drug development for glioblastoma.

Cleveland Clinic researchers led by Steven Rosenfeld, MD, PhD, believe that molecular motors such as myosins and kinesins are underappreciated as potential therapeutic targets for blocking tumor cell proliferation and migration in glioblastoma.

KIF11 Inhibitor Moves into Phase 2 Trials

Dr. Rosenfeld's team recently showed that inhibiting one molecular motor, the kinesin KIF11, with a small molecule blocked proliferation and invasion of glioblastoma cells and lengthened survival in mouse models of the malignancy. These findings identified KIF11 as a high-interest therapeutic target for treating glioblastoma, especially given the availability of a KIF11 inhibitor that is safe for human use.

Cleveland Clinic is collaborating with the German biopharma company 4SC to launch a phase 2 trial of a new KIF11 inhibitor for patients with newly diagnosed and recurrent glioblastoma. The trial is expected to begin enrollment by early 2017, with Cleveland Clinic as the sole U.S. site.

For a more detailed version of this article, see clevelandclinic.org/GlioblastomaMolecularMotors.

Study Suggests Breast Cancer Patients Need **More Counseling** About Fertility Preservation Options

Although advances in assisted reproductive technology have improved the ability of breast cancer patients to preserve their fertility prior to treatment, a Cleveland Clinic study has found that only a small percentage of patients received documented fertility counseling to explain and explore their options.

Dr. Valente is a breast surgeon in Cleveland Clinic Cancer Center's Comprehensive Breast Cancer Program and Assistant Professor of Surgery at Cleveland Clinic Lerner College of Medicine.

She can be reached at valents3@ccf.org or 216.444.0769.

On Twitter: @DrStephValente

In a retrospective chart review of women age 40 and younger diagnosed with breast cancer who were treated and followed at Cleveland Clinic between 2006 and 2014, less than one-third had a documented fertility discussion (FD) with their physician to review fertility preservation alternatives. Of those who did receive documented counseling, nearly 90 percent sought some form of fertility preservation, demonstrating the impact that formalized education sessions can have on cancer patients' childbearing choices.

While it is possible that some fertility preservation counseling took place without being documented in patients' electronic medical records, the research results nonetheless highlight the need to improve.

"This study brings awareness to healthcare professionals that we can do a better job of educating and discussing fertility options with patients and documenting it," says senior author Stephanie Valente, DO, a breast surgeon and Director of Cleveland Clinic Cancer Center's Breast Cancer Surgery Fellowship program. "In this world of documentation and electronic medical records, if it's not recorded, it did not happen."

The study results were presented at the 2016 American Society of Breast Surgeons Annual Meeting.

Discussing and Documenting Fertility Options

Breast cancer is the most frequently diagnosed form of cancer among women of reproductive age, according to the National Cancer Institute. Depending on dose and duration, chemotherapy, anti-hormonal therapy and radiotherapy can be ovotoxic, causing premature ovarian failure.

A range of new and increasingly effective strategies is available to preserve fertility in anticipation of breast cancer treatment, including:

- Oocyte and embryo cryopreservation
- Ovarian shielding and transposition
- Ovarian tissue cryopreservation and transplantation

Suppressing ovarian activity during chemotherapy, although controversial, may lessen the treatment's negative impact on fertility. Following treatment, in vitro fertilization (IVF) with banked autologous or donor oocytes or embryos may be used.

Discussion and consideration of those choices prior to treatment initiation, as well as recording the decision and outcome, is important. "Fertility preservation typically involves decisions made in advance of this therapy, with options being more limited once treatment is underway," Dr. Valente says.

"We need to document these discussions and make appropriate referrals to fertility specialists when necessary," she says. "The internet has helped make patients more informed consumers, and they should be aware of the fertility preservation options as part of their breast cancer treatment plan."

Considering the retrospective, observational nature of the study, Dr. Valente says it is possible that more fertility discussions are taking place than the statistics indicate. In some cases, physicians may have inquired about their patients' interest in fertility preservation but those patients' negative responses were not documented.

KEY POINTS

For breast cancer patients, chemotherapy, anti-hormonal therapy and radiotherapy can be ovotoxic, causing premature ovarian failure.

A range of new and increasingly effective strategies is available to preserve fertility in anticipation of breast cancer treatment.

A Cleveland Clinic study has found that only a small percentage of patients received documented counseling to explain and explore fertility preservation options.

A Closer Look at Study Results

Retrospective chart review was undertaken to identify all women age 40 and younger who were treated for breast cancer with chemotherapy and/or anti-hormonal therapy at Cleveland Clinic from 2006 to 2014. Researchers identified 303 such patients. The average age at diagnosis was 35.1 years. Thirty-two percent were single; 68 percent were married. Eighty-two (27 percent) had no children at the time of diagnosis.

Fertility preservation:

- After diagnosis, 80 of the full study cohort of 303 women (26 percent) had a documented FD.
- 9 of 80 (11 percent) of those having discussions chose no fertility options.
- 21 of 80 (26 percent) were prescribed gonadotropin-releasing hormone (GnRH) agonist for ovarian protection during chemotherapy.
- 55 of 80 (69 percent) had an IVF consultation, and 17 of 55 (31 percent) pursued oocyte retrieval. (Five patients had both GnRH agonist and an IVF consultation.)

Pregnancy after treatment:

- With a median follow-up duration of 3.7 years (range 4 months to 9.5 years), 22 of 303 patients (7 percent) became pregnant.
- Among those prescribed GnRH agonist alone, 5 of 16 (31 percent) became pregnant.
- Of those who pursued oocyte retrieval, 4 of 17 (24 percent) became pregnant via embryo transfer. Another 3 of 17 (18 percent) became pregnant without embryo transfer (2 of those 3 also were prescribed GnRH agonist).
- 3 of 9 patients (33 percent) who had a FD but did not pursue fertility preservation options became pregnant.
- 7 of the 223 women who had no documented FD became pregnant.

Overall, successful pregnancy was associated with younger age at the time of diagnosis and estrogen-receptor negative and progesterone-receptor negative tumors.

Dr. Valente notes that the median follow-up period of 3.7 years may be too short to include all fertility-related outcomes since most women undergo cancer treatment for approximately one to two years.

"With our follow-up, we may not have captured all the women who eventually did become pregnant," she says. "A 7 percent overall pregnancy rate after breast cancer treatment suggests that either we, as healthcare professionals, are not discussing fertility options enough, or maybe some of these women just wanted to wait a few more years to see how their prognosis turned out before they tried to have children."

Coordinating Care for Young Women with Breast Cancer

Fertility preservation counseling is one of many services provided by Cleveland Clinic Cancer Center's recently established Young Women's Breast Cancer Clinic. The clinic's multidisciplinary team assists young women throughout their diagnosis and treatment. Patients meet with a surgeon, medical oncologist, radiation oncologist, radiologist, plastic surgeon, psychosocial specialist, rehabilitation specialist, geneticist and fertility specialist.

"This all happens in one day, so it can be overwhelming for the patient," says Dr. Valente. "But the advantage is that her cancer treatment can begin immediately. When she leaves the clinic later that day, she has a treatment plan and there is no delay.

"Typically, it could take several weeks to see all of these different healthcare professionals to help develop a plan," she says. "Without such coordination of care, something could be missed — such as discussing your fertility options. We make sure that discussion takes place and that patients are aware of and understand all their alternatives."

Inotuzumab Ozogamicin Improves Outcomes for Relapsed/Refractory Acute Lymphoblastic Leukemia

Treating relapsed or refractory acute lymphoblastic leukemia patients with the antibody-drug conjugate inotuzumab ozogamicin (INO) produces significantly better results than does standard chemotherapy, with a higher rate of complete remission, less residual disease, and longer progression-free and overall survival, a recent clinical trial has found.

Dr. Advani is Director of the Inpatient Leukemia Program and a staff member of Cleveland Clinic Cancer Center's departments of Hematologic Oncology and Blood Disorders, and Translational Hematology and Oncology Research. She is also Associate Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

She can be reached at advania@ccf.org or 216.445.9354.

"Remission rates were much higher with INO versus what we would use as standard of care, and a much higher percentage of patients were able to proceed to stem cell transplant, which is the only known cure once a patient relapses," says Anjali Advani, MD, Director of Cleveland Clinic Cancer Center's Inpatient Leukemia Program and a co-author of the study published in the *New England Journal of Medicine.*

The findings are welcome news, since many acute lymphoblastic leukemia (ALL) patients relapse after first-line therapy and since salvage therapies are often unsuccessful in producing complete remission — typically a prerequisite for allogeneic hematopoietic stem cell transplantation.

The INO-VATE ALL Trial

The clinical trial, named INO-VATE ALL, was a phase 3 study designed to assess the safety and efficacy of single-agent INO compared with standard intensive chemotherapy for relapsed/refractory ALL. There is no single standard chemotherapy regimen for relapsed disease.

INO, an FDA-designated breakthrough drug for ALL, is an investigational antibody-drug conjugate comprised of an anti-CD22 monoclonal antibody linked to calicheamicin, a cytotoxic agent. CD22 is expressed in more than 90 percent of patients with B-cell ALL. When INO binds to CD22, it internalizes into the cell and releases calicheamicin, which exerts its cytotoxic effect by binding to the minor groove of the DNA, inducing double-strand breaks and apoptosis.

KEY POINTS

Relapsed/refractory acute lymphoblastic leukemia (ALL) has been difficult to treat, and novel therapeutic approaches are needed.

Recent research shows that the antibody-drug conjugate inotuzumab ozogamicin (INO) produces significantly better outcomes than does standard chemotherapy in relapsed/refractory ALL.

Hepatic adverse events due to INO therapy, particularly veno-occlusive disease, are a concern.

More research is needed to evaluate combining INO with other agents in upfront and relapsed/refractory ALL therapy.

"Relapsed/refractory ALL has been difficult to treat, and, in general, the remission rates with standard therapy have not been very high — between 30 and 50 percent," Dr. Advani explains.

Suboptimal outcomes in relapsed/refractory cases may be explained by the fact that lymphoblasts have developed resistance to multidrug-intensive first-line chemotherapy. "Many of the drugs we use at the time of relapse are similar to what we use for upfront treatment," Dr. Advani says. "There has been an unmet need for novel therapeutic approaches. With this study, the remission rates were much higher with inotuzumab versus what we would use as standard of care."

Remission and Survival Outcomes

Of the 326 patients in the study, 218 (109 in each group) were included in the primary intention-to-treat analysis of complete remission. The rate of complete remission was significantly higher in the INO group than in the chemotherapy group — 80.7 percent (95 percent confidence interval [CI], 72.1-87.7) versus 29.4 percent (95 percent CI, 21.0-38.8); $P < 0.001$.

Among patients who had complete remission, a higher percentage in the INO group than in the chemotherapy group had results below the threshold for minimal residual disease (0.01 percent marrow blasts) — 78.4 percent versus 28.1 percent; $P < 0.001$). The duration of remission was longer in the INO group than in the chemotherapy group — median 4.6 months (95 percent CI, 3.9-5.4) vs. 3.1 months (95 percent CI, 1.4-4.9); hazard ratio (HR) 0.55 (95 percent CI, 0.31-0.96); $P = 0.03$.

In the survival analysis, which included all 326 patients, progression-free survival was significantly longer in the INO group than in the chemotherapy group — median 5.0 months (95 percent CI, 3.7-5.6) versus 1.8 months (95 percent CI, 1.5-2.2); HR 0.45 (97.5 percent CI, 0.34-0.61); $P < 0.001$. The median overall survival in the INO group was 7.7 months (95 percent CI, 6.0-9.2) versus 6.7 months in the chemotherapy group (95 percent CI, 4.9-8.3); HR 0.77 (97.5 percent CI, 0.58-1.03); $P = 0.04$.

Veno-Occlusive Liver Disease Is a Concern

Hepatic adverse events, particularly veno-occlusive disease (VOD), were more common in the INO group than in the chemotherapy cohort. VOD $\geq$ grade 3 occurred in 13 patients (9 percent) treated with INO compared with one patient (1 percent) in the standard-therapy cohort. There were two treatment-related deaths due to VOD in the INO group, both after post-trial stem cell transplantation. The researchers determined that the transplant conditioning regimen may contribute to VOD risk, since treatment with a dual alkylator versus a single alkylator was the only significant covariate.

If the FDA approves INO, Dr. Advani expects that it will become a standard-of-care option for relapsed/refractory ALL. Blinatumomab, a bispecific T-cell-engaging antibody, already is approved for patients with relapsed/refractory ALL.

"There are advantages and disadvantages to both drugs," Dr. Advani says. "Blinatumomab does not have the risk of veno-occlusive disease, but patients have to be hooked up continuously to an infusion pump. They have to either have home care or be able to get back to the clinic every two days to get the pumps changed." INO is administered intravenously on a weekly basis for three weeks with each cycle.

Dr. Advani believes additional research is needed to evaluate combining INO with other agents, biologics or drugs in the upfront and relapse settings.

"The other issue for us to study is how we can best decrease the risk for veno-occlusive disease, in terms of the preparative regimen as well as the dosing and timing of INO," she says.

Solar Radiation-Induced Changes in MicroRNAs May Trigger Melanoma Progression

Cutaneous melanocytes in people with a history of melanoma react differently to sunburn-causing levels of solar radiation than do melanocytes in healthy people, Cleveland Clinic and Case Western Reserve University researchers have found.

Dr. Gastman is the Director of Cleveland Clinic Cancer Center's Melanoma Program, a staff member of the departments of Plastic Surgery and Immunology, and Associate Professor of Surgery at Cleveland Clinic Lerner College of Medicine.

He can be reached at gastmab@ccf.org or 216.444.2501.

Intense ultraviolet radiation (UVR) alters the balance of melanocytes' microRNA (miRNA) expression, inducing changes in cellular regulatory and immune-response pathways, the researchers discovered.

In healthy subjects, UVR exposure upregulates miRNAs, switching melanocytes to a protective mode.

In contrast, UVR downregulates miRNAs in the melanocytes of subjects who have had melanoma. That suppression triggers a network of genes involved in epithelial-mesenchymal transition and immune-response evasion, which the researchers speculate may represent the key first step in progression to melanoma. The UVR-mediated immune changes may help melanoma-prone melanocytes escape elimination while they accumulate the genetic and epigenetic alterations of malignancy.

The miRNA signature of this transitional phase could serve as the basis for a biomarker and help guide future treatment and prevention strategies, the investigators believe.

The research, published in *PLoS ONE*, marks the first time that scientists have observed the influence of UVR on melanocytes in their natural microenvironment, using tissue samples obtained by laser capture microdissection and analyzed with advanced genetic techniques.

The results suggest that melanocytes in melanoma-prone people have a defective miRNA biogenesis program and can acquire a cancer-promoting phenotype when tipped by environmental pressures such as UVR.

"We're finally getting to the bottom of why some people become more susceptible to melanoma while others do not," says study co-author Brian Gastman, MD, Director of Cleveland Clinic Cancer Center's Melanoma Program. "And we're building the basis from which one could develop treatment plans for prevention, so that we won't have to deal with melanoma after it becomes a deadly process."

MiRNAs' Widespread Regulatory Role

UVR previously had been shown to permanently alter melanocyte homeostasis and to have a direct mutagenic role in melanoma, but the molecular mechanism is unknown.

Environmental exposures such as UVR affect the level of regulatory miRNAs, which are small, noncoding RNAs that control the signal output of almost all cellular pathways. More than 1,000 miRNAs have been identified in humans, and they direct the expression of one-third of the human genome and affect a wide variety of processes.

MiRNAs dictate cellular responses by blocking translation or destabilizing messenger RNA, and are thus responsible for a type of gene silencing. Up- or downregulation of miRNAs respectively reduces or increases protein concentration in shared pathways or signaling cascades, including those involved in cellular differentiation, proliferation, inflammation, DNA repair, apoptosis and epithelial-to-mesenchymal transition (EMT).

In this way, miRNAs may help restore cellular processes in response to external stresses such as UVR. Conversely, miRNAs also have been implicated

KEY POINTS

Solar ultraviolet radiation (UVR) permanently alters melanocyte homeostasis and has a direct mutagenic role in melanoma, but the molecular mechanism is unknown.

A study analyzing the influence of UVR on melanocytes in their natural microenvironment shows that melanocytes in people with a history of melanoma react differently to UVR exposure than do melanocytes in healthy people.

UV irradiation can upset the balance of microRNA expression, triggering regulatory and immune-response changes in cancer-prone melanocytes that may represent the key first step in progression to melanoma.

The microRNA signature of this transitional phase could help identify at-risk patients and guide treatment and prevention strategies.

in the development of many cancers, including melanoma.

UVR Exposure Impacts Regulatory Networks

The Cleveland Clinic/Case Western Reserve team wanted to better understand UVR's impact on melanocytes and miRNAs and the oncogenic transition.

Previous studies of UVR's effects on melanocytes mostly were conducted using in vitro cell cultures, which may not reflect the way miRNAs respond in their normal in vivo microenvironment.

To address that, Dr. Gastman and his colleagues worked with skin tissue samples obtained from study participants and flash-frozen.

The participants were 17 women between the ages of 31 and 46 with Fitzpatrick skin types of I or II. Eight subjects had no medical or dermatologic history; nine had one prior primary melanoma.

A 6-mm circular area of skin on the posterior shoulder of each volunteer was irradiated with simulated solar UVR produced by a xenon arc lamp. The UVR dose was four times the amount previously determined to produce slight skin reddening. Twenty-four hours later, the irradiated area and an adjacent nonexposed site were punch-biopsied and cryopreserved. Using laser capture microdissection, investigators extracted melanocytes from the irradiated and nonirradiated samples for miRNA expression analysis.

The analysis found a striking difference in observed UVR-induced miRNA changes in the healthy women compared with subjects with a history of melanoma. A much higher proportion of miRNAs controlling key regulatory networks were downregulated in the melanoma patients than in the healthy subjects. In contrast, UVR miRNAs were predominantly upregulated in the healthy

(continued on page 22)

(CONTINUED)

subjects, suggesting that UVR exposure led to cancer-protective processes in their melanocytes.

The UVR-miRNA repression in the melanocytes of subjects with a history of melanoma released genes from inhibition, enabling probable gains of function. Further analysis of the affected gene/UVR-miRNA networks showed that they corresponded with well-known regulatory modules involved in controlling EMT and immune-response evasion processes. The functional outputs of these UVR-miRNA-regulated networks include critical immune-response evasive genes such as *PD-L1* and *PD-L2*.

Although EMT and immune-response evasion are intrinsic to melanoma's invasion-metastasis cascade, before this research they had not been connected to the effects of UVR exposure on miRNA expression. "Our results strongly indicate that some form of immunosuppression is prematurely occurring in the UV-irradiated melanocytes of patients as opposed to those of healthy persons," Dr. Gastman says.

In essence, the findings show UVR-induced miRNA downregulation is capable of initiating phenotypic changes in melanocytes of melanoma patients that are not apparent in healthy subjects' melanocytes. These phenotypic changes — such as apoptosis resistance and the ability to migrate — have the potential to confer stem cell-like properties to melanoma-prone melanocytes in subjects with a history of the disease, and may allow the cells to accumulate mutations that result in malignant transformation.

The Value of In Vivo Research

While the research involved a relatively small number of volunteers, it is significant in that most studies reporting on UVR-associated molecular changes in melanoma refer to mouse or in vitro models. The analysis of human melanocytes obtained from their microenvironment after controlled UVR exposure was a complex undertaking that adds significantly to the knowledge base, Dr. Gastman says.

The decision to conduct the study in young women involved practical, enrollment-related considerations as well as issues of epidemiologic and scientific interest, according to Dr. Gastman. Epidemiologic data have suggested that gender and genetics may influence the distribution of melanoma on the skin surface, and histopathologic characteristics of the lesion and age-specific melanoma incidence rates are greater among women than men younger than 40 at diagnosis.

Screening and Treatment Implications

With the improved understanding of how melanocyte miRNAs respond to UVR, researchers are closer to developing a predictor of melanoma risk, which may ultimately lead to targeted prevention and novel early therapies for high-risk populations.

"Having a miRNA signature indicating that a genetic switch has been flipped, which is what we see here, might change the way we evaluate patients," Dr. Gastman says.

Being able to stratify patients as high-, intermediate- or low-risk is important in order to appropriately utilize medical resources. "It's not just about treating melanoma — it's also about preventing melanoma, which is a huge burden in the United States," he says.

New Staff

Scott R. Steele, MD
Chairman, Department of Colorectal Surgery

Background: Graduated from United States Military Academy at West Point (1994). Medical degree from University of Wisconsin (1998). Residency in general surgery at Madigan Army Medical Center (2003) and fellowship in colon and rectal surgery at University of Minnesota Medical Center (2005). Active military duty from 1998 to 2015, including four combat deployments in Iraq and Afghanistan as a trauma surgeon, and serving at Madigan Army Medical Center as a colorectal surgeon and Associate Program Director of the General Surgery Residency Program. Most recently was Division Chief of Colorectal Surgery at University Hospitals Cleveland Medical Center, as well as Vice Chairman of Clinical Affairs and Associate Director of Surgical Services for the Digestive Health Institute.

Specialty interests: Clinical outcomes research, minimally invasive surgery, colorectal cancer

Research interests: Epidemiological and outcomes-based research on colorectal disease: cancer, inflammatory bowel disease, pelvic floor disorders, endoscopy and anorectal disease.

Eberechi Sandra Agwa, MD
Regional Oncology

Dana Angelini, MD
Hematology/Oncology

Jeremy Donaghue, MS, DABR
Project scientist

Jessica Geiger, MD
Hematology/Oncology

Bingqi Guo, PhD
Radiation Oncology

Mohamad Khasawneh, MD
Regional Oncology

Omar Mian, MD, PhD
Radiation Oncology

Aziz Nazha, MD
Hematology/Oncology

Saju Rajan, MD
Radiation Oncology

Jacob Scott, MD
Mathematical Oncology/ Radiation Oncology

Michael Weller, MD
Radiation Oncology

Neil Woody, MD, MS
Radiation Oncology

Save the Date

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March 10-11, 2017

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Orlando, Florida
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April 22, 2017

Advances in the Multidisciplinary Management of Lung Cancer: From Screening to Immunotherapy
InterContinental Hotel and Conference Center Cleveland
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May 11-12, 2017

2017 Cleveland Breast Cancer Symposium
InterContinental Hotel and Conference Center Cleveland
For more information: kralls2@ccf.org

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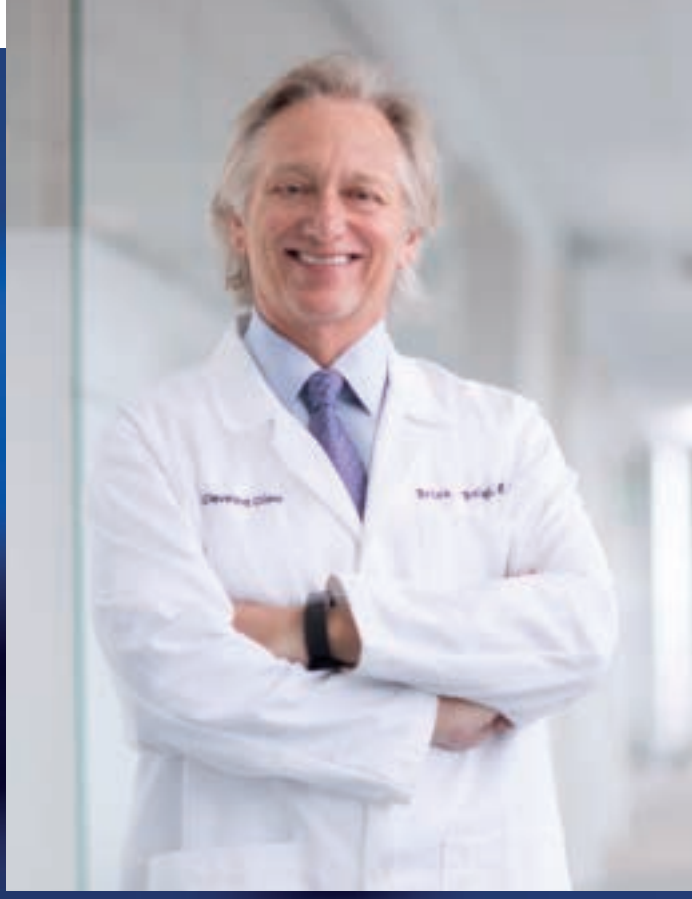
CHAIRMAN'S **Q&A**

Brian J. Bolwell, MD, FACP, Talks About **Time to Treat**



Dr. Bolwell is Chairman of Taussig Cancer Institute.

He can be reached at bolwelb@ccf.org or 216.444.6922.

On Twitter: @clebmt

Cleveland Clinic Cancer Center is working intensely to reduce time to treat, the interval from when a patient is diagnosed with cancer to when they begin to receive care. Why?

Because it is the right thing to do. Because cancer is associated with more fear than any other diagnosis, and that fear gets magnified the longer a patient and their family wait to begin treatment. If you have just been diagnosed with colon cancer and are asked when you want to have surgery, no one would say, "Let's wait a couple of months." Everyone would say, "As soon as possible."

Is there any indication that prolonged time to treat has a clinical impact?

Studies have shown that it may be associated with deleterious outcomes in at least two cancers: lung cancer and head and neck cancer. Part of the challenge is the relative lack of data. We are starting to look at the impact using the National Cancer Database, which comprises millions of cancer patients. We have found that, especially for early-stage cancers, there is a statistically significant decrease in survival by the number of weeks you delay initial therapy. Nobody has known that. We are going to publish it, and I think it will raise the sense of importance.

What do data show about treatment wait times for cancer patients?

The average time to treat nationally appears to be getting worse by the year. Shockingly, it is worst of all at the leading academic centers. Among Comprehensive Cancer Centers, it is 43 days. I would argue that is at least several weeks too long.

Why do large academic cancer centers have long wait times for treatment?

A lot of them probably don't know that these data exist, so there is a lack of awareness. It is also a big ecosystem. Getting access to the operating room might not be as efficient. Physicians go away to give talks or to a research symposium. We have started to look at our program, and a big part is access. There might be 80 different points of access just to enter the system. Another reason time to treat is getting worse by the year is the insurance industry is increasingly requesting pre-authorizations for almost everything we do, including imaging. As an example, in lung cancer, it is fairly routine for insurance companies to be granted 14 days to give a pre-authorization for a bronchoscopy. That doesn't make any clinical sense, and it doesn't make any sense from a psychological perspective for the patient.

Given those complexities, how have you approached trying to reduce time to treat?

One step at a time. There are countless opportunities. Every part of our Cancer Center is working to make these results better. A few examples: When a cancer patient is assigned a surgeon, historically that becomes a linear process. The surgeon has x amount of availability in the operating room, or may be traveling, whatever. Alternatively, if you could be assigned to one of a group of surgeons, all with outstanding expertise, then potentially you could be assigned on the basis of which surgeon has quicker access to the operating room. We are starting to explore that. In radiation therapy, we have reduced time to treat by two to three days, based on reducing pre-authorizations or simply by being more efficient internally.

Part of the challenge in a big campus like we have, and like most comprehensive cancer centers have, is literally getting from Point A to Point B. It can get confusing. It can be a challenge for people who are infirm. Our new cancer building is going to allow the different components of our program to be in the same physical location. It is built to

deliver accessible, coordinated care. When you have radiation therapists, medical oncologists and surgeons all in the same place, ideally at the same time, that in itself will manage a lot of this.

One of the things we are focused on is eliminating outliers. When we started this process, about 17 to 19 percent of our patients had a time to treat of more than 50 days. That is way too long. If we can eliminate that, it will obviously bring the entire population's mean down. I am personally obsessed with the unfortunate soul who gets lost in the system. We want that number to be zero. We have hired navigators for many of our programs. They know the identity of every patient who is diagnosed with cancer, and make sure that no one gets lost in the system or waits an undue amount of time.

That's especially important considering that treatment delays inordinately affect vulnerable populations — the poor, elderly and minorities.

There is no question that cancer outcomes correlate with socioeconomic status and whether a patient has insurance. By having liaisons make sure that patients can get from Point A to Point B and get the best care, we can try to alleviate those disparities, and we are.

Have you been able to reduce time to treat?

It is down to around 30 days, so we have cut about 10 days. We are currently being led by our breast cancer program, which is in the low 20s. I want to get it below 20 days for every program. I want that to be consistent. I think that the challenge is not just achieving the result, but maintaining it. We are trending in the right direction. I think we are going to become leaders in the field. The work isn't done, but every time we identify an opportunity we can make it better, and that's what we are doing.

What advice about reducing time to treat would you offer other institutions?

Step one is you have to care about it. It has to make sense to you, and it has to be part of your culture. The nice thing about Cleveland Clinic, and the reason most of us work here, is that we are a very patient-oriented culture. We have a slogan that says "Patients First," and we mean it.

The second thing you have to do is measure your time to treat. It isn't easy. It is not embedded in the electronic medical record, and we have had to use resources to calculate it. That is the right thing to do.

The third thing is you cannot tackle this physician by physician. It has to be a team approach. You have to have the programs work together; you have to supply them with data; you have to share best practices.

The fourth thing is to identify your barriers. What are the challenges? What are the obstacles? We have extensive experience utilizing continuous improvement techniques and teams.

Reducing time to treat is a very complex process, but it is a wonderful way to illuminate what happens on a patient's journey, much of which an individual physician may not be aware of.

Cleveland Clinic Cancer Center's new cancer care facility will open in March. Its unique design consolidates cancer treatment and support services in one location for maximum convenience, in a serene, spacious setting filled with light and hope. Features include:

Exam rooms near multidisciplinary clinical work areas, so that patients remain in one place for appointments with multiple specialists on their treatment team

Private and semi-private chemotherapy infusion suites with space for family members and floor-to-ceiling windows overlooking green areas

A large on-site hematology laboratory and collecting stations to eliminate waits for blood testing

A retail pharmacy stocked with items to meet cancer patients' needs

On-site advanced diagnostic imaging and radiation therapy facilities

Patient services including a café whose menu accommodates special dietary needs, a wellness center, spiritual area, wig boutique, and art and music therapy facilities.

A dedicated monitoring area for patients participating in phase I clinical trials

For more on this new cancer care facility, visit clevelandclinic.org/taussigcancercenter.

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Cleveland Clinic Cancer Center provides complete cancer care enhanced by innovative basic, genetic and translational research. It offers the most effective techniques to achieve long-term survival and improve patients' quality of life.

The Cancer Center's more than 450 physicians, researchers, nurses and technicians care for thousands of patients each year and provide access to a wide range of clinical trials. Cleveland Clinic Cancer Center unites clinicians and researchers based in Taussig Cancer Institute and in Cleveland Clinic's 26 other clinical and special expertise institutes, as well as cancer specialists at our regional hospitals, health centers and at Cleveland Clinic Florida. Cleveland Clinic is a nonprofit academic medical center ranked as the No. 2 hospital in the country (*U.S. News & World Report*), where more than 3,400 staff physicians and researchers in 140 specialties collaborate to give every patient the best outcome and experience.

Cleveland Clinic

The Cleveland Clinic Foundation
Cleveland Clinic Cancer Center
9500 Euclid Ave. / AC311
Cleveland, OH 44195

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