

INNOVATIONS

in Cancer



Evidence-Based Medicine for Radiation Oncology pg 4

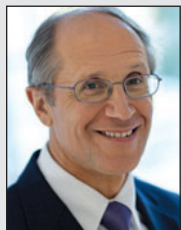
A new approach to a breast cancer vaccine	pg 3
Translating basic science into innovative research	pg 6
Overcoming barriers to clinical trial participation	pg 7



University Hospitals Case Medical Center and Case Western Reserve University School of Medicine are consistently recognized as two of the premier institutions in the nation, according to U.S. News & World Report's annual rankings.

Director's Corner

Bringing Innovation in Clinical Trials to the Forefront



In this issue of *Innovations in Cancer*, we focus on our clinical research. High-quality cancer care requires protocols. Not every patient is a candidate for a clinical trial, but often our best care comes from having a patient participate in one. Every cancer center strives to make clinical trials critical to its mission.

What is special about University Hospitals Seidman Cancer Center is our commitment to bringing innovation in clinical trials to the forefront. This allows us to offer our patients newer treatments using the most innovative approaches and to integrate all aspects of clinical therapy – including drugs, vaccines, radiation and surgery – so that we can bring forward the best new approaches to cancer care, many of which are tested for the first time at our center.

In recent years we have recruited **Neal J. Meropol, MD**, and **Mitchell Machtay, MD**, to augment the ongoing efforts of **Afshin Dowlati, MD**. We are fortunate to have such nationally recognized leaders in cancer care and clinical trials, who have catapulted our center to the leading edge of innovation.

The cover story highlights the efforts of Dr. Machtay to emphasize evidence-based medicine in clinical trials of advances in radiation oncology through his leadership in the Radiation Therapy Oncology Group (RTOG) and the new cooperative that RTOG is joining, NRG Oncology.

Also in this issue, **Joseph Baar, MD, PhD**, describes a breast cancer clinical trial based on a fresh approach to vaccine design. This vaccine targets supporting vasculature instead of molecular signatures on the cancer cell. Dr. Dowlati explains how the interactions of clinicians and basic scientists inform the development of important early-phase clinical trials. He highlights examples of studies led by three junior faculty members from Case Western Reserve University School of

Medicine: **Paolo Caimi, MD**; **Jennifer Eads, MD**; and **Neelesh Sharma, MD**. Dr. Meropol highlights a joint NCI-ASCO symposium and the publication arising from it that discusses proven interventions to facilitate trial enrollment and to identify additional research needs. One of those interventions comes out of a trial he led to identify and overcome patient barriers. Finally, **Andrew Sloan, MD, FACS**, describes a Phase I trial of a novel way to confer protection against a dose-limiting toxicity in glioblastoma. He is employing a viral vector to insert a gene into bone marrow that may enable the use of more potent chemotherapy regimens.

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Contact Us

We have many trials, including early-stage trials, linked to our innovative approach to care. We would be glad to discuss interest or questions about these trials. You can contact any of the physicians listed in this issue. A more complete listing of our current trials can be found at **UHSeidman.org**.

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The commitment to exceptional patient care begins with revolutionary discovery. University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a national leader in medical research and education and consistently ranked among the top research medical schools in the country by U.S. News & World Report. Through their faculty appointments at Case Western Reserve University School of Medicine, physicians at UH Case Medical Center are advancing medical care through innovative research and discovery that bring the latest treatment options to patients.

A New Approach to a Breast Cancer Vaccine

Researchers explore whether targeting vasculature will improve vaccine design

■ By Joseph Baar, MD, PhD, FRCP(C), FACP



Joseph Baar, MD, PhD, FRCP(C), FACP, Director of Clinical Breast Cancer Research and Breast Cancer Survivor Program, UH Seidman Cancer Center at UH Case Medical Center; and Associate Professor of Medicine, Case Western Reserve University School of Medicine

Although many novel therapies have been explored for metastatic breast cancer, unfortunately an unacceptably high number of women continue to die from it. A compelling need exists for new treatments for advanced disease, including cancer vaccines.

With support from a Susan G. Komen® research grant of close to \$1 million to Case Western Reserve University School of Medicine, we will be testing an innovative vaccine strategy for metastatic breast cancer that generates killer T cells. These T cells ignore the cancer cells altogether and instead target the supporting vasculature.

Breast Cancers Evaded Earlier Vaccines

Despite concerted efforts to develop a successful breast cancer vaccine, researchers have repeatedly met with failure because the cancer cells evade immune cells by either changing or not expressing the molecular targets that the immune cells seek. Our vaccine offers a new strategy, targeting elements on the surface of the vasculature. This approach stops the growth of tumors by blocking their blood supply. The vaccine has an additional potential advantage: It may be useful in many types of metastatic breast cancers because it focuses on the vasculature, not tumor-specific markers.

Dendritic cells (DC) are the most potent antigen-presenting cells for generating sensitized T cells. Appropriate antigens can be loaded onto DC, which are then injected into patients to create a specific immune response. We will be using a tumor blood vessel antigen (TBVA) peptide-pulsed DC vaccine (alphaDC1) to immunize patients. Patients must be HLA-A2 positive because the TBVA peptides are specific for HLA-A2 molecules and would not bind to other HLA molecules.

Who is Eligible?

Patients must have metastatic breast cancer and must be HLA-A2 positive. No exclusions will be made for prior breast cancer treatment, but patients must not be steroid-dependent or have an underlying autoimmune disease. We will perform HLA typing, a simple blood test, for interested patients who meet the other criteria for participation.



From prior research, we know that a patient's regulatory T cells and myeloid-derived suppressor cells may suppress immunity. Gemcitabine, a treatment for metastatic breast cancer, has proven effective in downregulating the activity of these cells and mediating enhanced immunity to immunotherapy. Therefore, all patients will receive gemcitabine prior to vaccination.

Pilot Study Will Enroll 30 Women

A total of 30 patients will be enrolled in this four-year, single-arm, prospective clinical trial of DC vaccination. In conjunction with co-investigator Walter J. Storkus, PhD, at the University of Pittsburgh School of Medicine, we will initially enroll 15 patients. Results from this group will enable us to determine the best time to administer the vaccine after chemotherapy. We will then treat a second group of 15 patients using this optimal time point.

When earlier studies were performed with a similar vaccine, researchers were concerned that targeting tumor vasculature might lead to an increased risk of bleeding, but this did not occur in patients with other types of cancer. We anticipate that the vaccine's target antigens may be more exposed in tumor vasculature than in normal vasculature.

Our early data suggests that this research in vaccine development will become a new path to treating metastatic breast cancers. For more information, contact me at Joseph.Baar@UHhospitals.org.

Evidence-Based Medicine: Increasingly Critical for Radiation Oncology

Clinical trials will fill research gaps in several areas

■ By Mitchell Machtay, MD



Mitchell Machtay, MD, Chairman, Department of Radiation Oncology, UH Seidman Cancer Center; and Vincent K. Smith Professor of Radiation Oncology, Case Western Reserve University School of Medicine

Dr. Machtay is also Deputy Chair of the Radiation Therapy Oncology Group (RTOG) and Chair of its Research Strategy committee. He is assuming the role of Group Deputy Chair for Research Strategy and Chair of the Research Strategy Committee for the new cooperative group. (See sidebar.)

Evidence-based medicine (EBM) is important for all aspects of oncology, including radiation oncology. In particular, investigators must fill in the many research gaps left by a focus on drug treatments. While these studies in oncology drug development are beneficial, more research needs to concentrate in other areas, such as radiation oncology procedures, new technologies in radiation, and radiation dosage and scheduling. These aspects of radiation oncology have great impact on cancer patients' potential disease-free survival and cure. Keep in mind that 50 percent of all patients with cancer receive radiation as part of their treatment, and more than two-thirds who are treated with radiation are treated with curative intent.

To improve cure rates, we need high quality evidence-based research into new approaches and new technologies.

RTOG Emphasizes Evidence-Based Medicine

The Radiation Therapy Oncology Group (RTOG) is an international consortium of radiation oncologists and other investigators involved in radiotherapy clinical research. Funded by the National Cancer Institute (NCI), RTOG leads 30 to 40 national clinical trials at any given time. These studies emphasize EBM, with Phase 2 and Phase 3 randomized trials designed to establish the standard of care for patients with cancer. In an exciting development, RTOG is merging with two other groups to form a new "super group" called NRG Oncology. (See sidebar.) Researchers at University Hospitals Seidman Cancer Center and Case Western Reserve University School of Medicine are playing key roles in RTOG and will continue to do in NRG Oncology.

RTOG's biggest achievement has been the optimization of combined modality therapy (radiation plus systemic therapy and surgery where appropriate) to improve cure rates for many solid tumors, including cancers of the head and neck, lung, gastrointestinal system, prostate and brain.

Stereotactic Radiosurgery

Stereotactic radiosurgery has been an important advance in cancer treatment. RTOG led a landmark clinical of stereotactic radiosurgery in the late 1990s, which demonstrated that adding radiosurgery to standard whole brain radiation improved outcomes in patients with brain metastases, especially those with only one brain lesion. The data also showed in a rigorous, scientific, evidence-based fashion that radiosurgery improved the lives of people with cancer.

The potential advantage of radiosurgery is that the radiation dose is targeted at the tumor itself with pinpoint accuracy, with less scattered radiation to healthy tissues. This allows a higher dose of radiation to be delivered each day — as much as five to eight times more than is given during conventional radiation treatment. As a result, the patient may need only three to five radiation treatments, a great convenience. Most importantly, radiosurgery improves the quantity and quality of survival.

We continue to test radiosurgery with rigorously designed clinical trials and protocols, using well-defined eligibility requirements, carefully standardized quality assurance of the treatment itself and very well-defined metrics for follow-up. The outcome measures go beyond traditional calculations of progression-free and disease-free survival to include patient-reported outcomes related to quality of life and side effects.

Clinical Trial of Radiosurgery

One of the most exciting RTOG trials in which I participated tested three treatments of radiosurgery

A New Cooperative Group – NRG Oncology

The National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG) and the Gynecologic Oncology Group (GOG) have taken formal steps to merge and form a new cancer clinical cooperative group called NRG Oncology (nrgoncology.org). The three legacy groups will continue to carry out NCI-supported trials as independent but collaborative entities through February 2014. Pending anticipated funding by the NCI, NRG Oncology will officially manage its federal research activities as the new cooperative beginning in March 2014.

An RTOG trial demonstrated that there is a limit to how much radiation can be given with conventional intensity-modulated radiation therapy (IMRT) in patients with stage 3 lung cancers. Increasing IMRT did not increase the cure rate in this group; in fact it had the opposite effect.

(as compared with historical treatment with 30-40 conventional radiation treatments) for medically inoperable stage 1 non-small cell lung cancer (NSCLC) in patients who were elderly or too ill for surgery. The conventional approach destroyed the lung tumor 50 percent of the time, while stereotactic radiosurgery achieved this 90 percent of the time. Side effects with radiosurgery were very tolerable in this frail patient population. We are looking to further improve outcomes, possibly by adding other types of treatment. We are also studying radiosurgery for cancers of the liver and prostate, brain tumors, and metastatic disease to the spine.

The Next Generation

We will be starting clinical trials using proton beam radiation, the next generation of radiation technology. Proton beam radiation should absolutely be used in certain settings, most importantly in pediatric and adolescent/young adult cancers, because the radiation doses and protection of normal tissues are better. Its use for many other types of cancers needs further rigorous study, however.

One such use is in lung cancer. An RTOG trial demonstrated that there is a limit to how much radiation can be given with conventional intensity-modulated radiation therapy (IMRT) in patients with stage 3 lung cancers. Increasing IMRT did not increase the cure rate in this group; in fact, it had the opposite effect.

This is an excellent example of why we need more evidence-based research. The trial clearly showed that we cannot assume more radiation will be more

effective. We hope that a large, multicenter trial of proton beam therapy versus conventional IMRT in lung cancer will give us more answers. Our own proton beam facility, for which we have already broken ground at the UH Seidman Cancer Center, is expected to open in 2015, allowing our researchers to develop and participate in clinical trials using this next generation of radiation technology.

Looking to the Future

During 100 years of the use of radiation for cancer, and 45 years of RTOG trials, we have only scratched the surface of radiation technologies and their potential benefits for our patients. New advances are occurring rapidly, and by combining these with new systemic therapies and new surgical approaches, we look forward to providing the best chance for remissions and cures for our patients with solid tumors.

For more information, contact me at
Mitchell.Machtay@UHhospitals.org.

Innovations in Research

Early-Phase Clinical Trials: Close Collaboration Among Clinicians, Scientists

Investigators translate basic science into innovative clinical studies

■ By Afshin Dowlati, MD



Afshin Dowlati, MD, Lucile and Robert H. Gries Endowed Director, Center for Cancer Drug Development, University Hospitals Seidman Cancer Center; Rosalie and Morton A. Cohen Chair in Lung Cancer; Director, Phase I & Thoracic Oncology Programs, UH Seidman Cancer Center; Professor of Medicine, Case Western Reserve University School of Medicine; and Co-Leader, Developmental Therapeutics Program, Case Comprehensive Cancer Center

Drug discovery with the aim of finding effective new anti-cancer drugs is what we do at the Center for Cancer Drug Development (CCDD) at University Hospitals Seidman Cancer Center. We are proud to be one of 14 specialized centers across the U.S. that have been granted National Institutes of Health (NIH) funding through the School of Medicine for this type of work.

In our center, our clinicians and basic scientists work closely throughout the drug development and clinical trial process. These interactions inform our clinical trials in real time so that we can quickly adapt and do what is best for drug development and for our patients.

Three of our current studies show how we leverage promising results from our basic drug development research to create innovative early-phase clinical trials.

Research in Hematologic Malignancies and Solid Tumors

Methoxyamine (TRC102), developed by **Stanton L. Gerson, MD**, at Case Western Reserve University School of Medicine, potentiates the effects of both fludarabine and temozolomide by blocking cellular repair of drug-induced DNA damage. **Paolo Caimi, MD**, and **Jennifer Eads, MD**, Medical Oncologists, UH Seidman Cancer Center, and Assistant Professors, Medicine, Case Western Reserve University School of Medicine, have developed clinical trials using this agent.

Dr. Caimi is completing a Phase I clinical trial testing fludarabine with methoxyamine for treatment of hematologic malignancies in patients who have relapsed after at least one line of therapy (**ClinicalTrials.gov** Identifier: NCT01658319). The drug combination appears safe in these initial studies, with no observed dose-limiting toxicities. Patients are now being enrolled at the highest planned methoxyamine dose.

Dr. Eads has begun a Phase I pharmacokinetic study of temozolomide plus methoxyamine (CASE1Y05). Patients with any type of solid tumors, CNS or non-CNS, are eligible if they have progressed on all other lines of therapy or if temozolomide would be a reasonable treatment option. Early results are promising. She is enrolling six additional patients in the non-CNS tumor arm and additional patients in several remaining dose levels in the CNS tumor arm.

A New Approach in Advanced NSCLC

Neelesh Sharma, MD, PhD, Medical Oncologist, UH Seidman Cancer Center, and Assistant Professor of Medicine, Case Western Reserve University School of Medicine is currently enrolling patients with advanced non-small-cell lung cancer (NSCLC) with disease progression after chemotherapy in the Phase I portion of a Phase I/II clinical trial of erlotinib in combination with quinacrine in (CASE8512).

Erlotinib's clinical benefit in patients with wild type EGFR is transient (two to three months) and variable due to resistance that may be linked to high activity of the nuclear factor- κ B (NF- κ B) pathway. Research in basic science revealed that the anti-malarial drug quinacrine can restore the activity of the tumor suppressor protein p53 while simultaneously suppressing activation of NF- κ B. This led to the idea of adding quinacrine to erlotinib in patients with advanced NSCLC. In preclinical testing, the combination of quinacrine and erlotinib was more effective than erlotinib alone in both lung cancer cell lines and a mouse model.

Dr. Sharma has also used whole genome microarray analysis to identify a set of genes that could potentially serve as a biomarker to predict response to this drug combination. He will test this hypothesis as part of the Phase II portion of the trial.

These trials that employ drugs like methoxyamine and quinacrine are excellent examples of how we take basic science discoveries and developed early-phase clinical trials for cancer patients at CCDD.

For more information, contact us at **1-800-641-2422**.



Dr. Afshin Dowlati meets weekly with the Phase I research team to discuss progress of clinical trials.

Overcoming Barriers to Clinical Trial Participation

Evidence-based approaches can improve enrollment

■ By Neal J. Meropol, MD



Neal J. Meropol, MD, Lester E. Coleman, Jr. Chairman of Cancer Research and Therapeutics; Chief, Division of Hematology and Oncology, Seidman Cancer Center at UH Case Medical Center; Professor of Medicine, Case Western Reserve University School of Medicine; Associate Director for Clinical Research, Case Comprehensive Cancer Center

Ensuring adequate patient participation in clinical trials is a major concern for oncology researchers. In 2010, the National Cancer Institute (NCI) and the American Society of Clinical Oncology (ASCO) co-sponsored a symposium that brought together 358 experts to discuss proven interventions to facilitate trial enrollment and to identify additional research needs. A recent publication discusses evidence-based recommendations arising from the meeting and the current literature that supports them. **(See sidebar.)** As one of the symposium organizers, I am pleased to share some of our NCI-sponsored research featured in this important discussion.

Education to Address Patient Barriers

We carried out a randomized trial of a Web-based, personally tailored, interactive program designed to address patient barriers to clinical trial participation (J Clin Oncol. 2013;31(suppl);abstr 6500). The program, called PRE-ACT (Preparatory Education About Clinical Trials) was conducted at the University Hospitals Seidman Cancer Center in conjunction with four other sites. The trial addressed individual knowledge and attitude barriers before each patient's first oncologist visit, so that the patient would be better prepared to consider clinical trials as a treatment option.

A total of 1,255 patients were randomly assigned to one of two study arms. Both arms included an initial Web-based assessment of individual barriers to clinical trials. We gave patients in the PRE-ACT arm access to an online video library with 30- to 90-second clips



Dr. Neal Meropol has published extensively on barriers to clinical trial enrollment.

intended to address the barriers specific to each patient. The patients in the control arm received high-quality general educational text about clinical trials excerpted from the NCI website.

PRE-ACT Intervention More Effective

We identified many patient barriers, including concern about side effects of study treatments, worry about receiving placebo instead of medication, health insurance concerns, and reluctance to ask about trials unless the doctor brought it up first.

Our results demonstrate that PRE-ACT's computer-based approach can help patients overcome these barriers by improving their knowledge, attitudes and preparation for decision-making about clinical trials. The PRE-ACT approach was more effective than NCI text in improving knowledge and reducing attitudinal barriers, and was associated with greater patient satisfaction.

A secondary analysis released in October 2013 (35th Annual Meeting of the Society for Medical Decision Making, Baltimore, MD) found that patients with more financial concerns about trial participation had greater distress and decisional conflict, and lower self-efficacy and preparation for decision-making than patients with less concern about finances.

We hope that the information from the NCI-ASCO symposium and results from research trials of interventions like PRE-ACT will help speed progress against cancer by enhancing patient participation in clinical trials.

For more information, contact me at Neal.Meropol@UHhospitals.org.

NCI-ASCO Recommendations

"The National Cancer Institute–American Society of Clinical Oncology Cancer Trial Accrual Symposium: Summary and Recommendations" was published in the *Journal of Oncology Practice* in October, 2013.

Recommendations for evidence-based best practices that focus on patients and their communities include considering the patient's perspective and potential barriers when reviewing and implementing trials; simplifying informed consent documents; clarifying possible patient financial liabilities; using culturally appropriate educational materials; involving advocates/advocacy organizations in the educational process; engaging underserved communities; involving community leaders in the design and implementation of trials that are important to them; exploring the use of social media, patient registries and electronic databases; providing access to peer mentors and patient navigators; and including multilingual staff and medical interpreters on the research team.

Many additional recommendations in the paper address evidence-based best practices for physicians/providers and clinical trial sites, as well as future research needs.



Innovations in Research

A Novel Gene Therapy Trial Holds Promise for Treatment of Newly Diagnosed GBMs

Using a viral vector to confer protection against dose-limiting toxicity

■ By Andrew Sloan, MD, FACS



Andrew Sloan, MD, FACS; Director, Brain Tumor and Neuro-Oncology Center, and Peter D. Cristal Chair in Neurosurgery, UH Seidman Cancer Center at UH Case Medical Center; and Associate Professor, Case Western Reserve University School of Medicine

Glioblastoma multiforme (GBM) is a deadly tumor with a median survival of less than one year from diagnosis, even with aggressive treatment. Current standard of care is maximal neurosurgical resection followed by radiation and chemotherapy with alkylating agents such as temozolomide (TMZ). The probability of surviving two years is only about 25 percent, and the disease is very difficult to manage once it recurs.

At University Hospitals Seidman Cancer Center, we have initiated an innovative trial for the treatment of GBM. The hope is that employing a viral vector to insert a gene into bone marrow will enable oncologists to administer more potent chemotherapy.

More Effective Treatment Also Suppresses Bone Marrow

TMZ exerts its antitumor effect through DNA methylation, but a tumor gene that codes for MGMT, an enzyme that repairs methylation, enables the tumors to survive despite the chemotherapy. Overall, patients do live twice as long after receiving TMZ as they would without treatment, but this is true only if their tumor does not contain this common resistance gene.

We now know the drug O6-benzylguanine (BG) will inhibit tumor MGMT activity. The combination of TMZ/BG can be used against tumors that contain the resistance gene. Unfortunately, patients cannot tolerate much TMZ/BG because BG also blocks MGMT activity in healthy bone marrow. This leads to major dose-limiting toxicities, including Grade III-IV thrombocytopenia and neutropenia.

Trial Inserts Protective Gene

Two decades ago, Stanton L. Gerson, MD, Director of UH Seidman Cancer Center and Case Comprehensive Cancer Center, identified and pioneered studies of a mutated MGMT molecule that does not help tumors resist TMZ/BG. In our Phase I clinical trial, we are transferring the gene that codes for this protective, mutated MGMT into patients' normal bone marrow stem cells and grafting them back into the bone marrow. We hope the mutated MGMT will block the development of BG's dose-limiting toxicity in the bone marrow, but not impair TMZ/BG effectiveness in tumor cells elsewhere in the body.

We use a leading-edge gene therapy technology that employs a lentivirus as a vector. (Disclosure: This technology was patented by Dr. Gerson and Case Western Reserve University and was then licensed to Lentigen, which will supply the lentivirus vector for the gene therapy clinical trials.) The trial includes a dose-escalation study of TMZ/BG. Bone marrow toxicity will be closely monitored.

We enrolled the first patient in December 2011. To date we have enrolled six patients and plan to enroll up to 18.

In our experience, the treatment is reasonably well tolerated. We are pleased with how the viral vector approach to gene transfer is working, and the amount of genetically engineered stem cells getting into blood and bone marrow is improving.

A recent paper described a trial that employed a similar strategy but used a less effective (non-Lentigen) vector. The approach increased survival, an encouraging result for our study.

We are very excited about this trial because the gene transfer approach may ultimately allow us to use higher, and hopefully more effective, doses of chemotherapy to treat GBM.



Trial Enrollment

We are enrolling patients with newly diagnosed GBM shortly after they undergo initial surgery but before they receive any other treatment. We welcome inquiries from oncologists and their patients. You may contact the office of Andrew Sloan, MD, at **216-844-6054** or **Andrew.Sloan@UHhospitals.org**.