Nanotechnology: Small Particles Make Huge Impact on Cancer Medicine

Also inside:

Highlights from the American Society for Clinical Oncology Annual Meeting
Dear Colleagues,

Welcome to the latest edition of Taussig Cancer Institute’s Cancer Consult! I hope you find this issue informative and inspiring.

Innovation takes many forms as we look to the future of cancer care. In our cover story, we describe the exciting work our researchers are doing in the emerging field of nanotechnology. These tiny drug-delivery particles can hone in on cancer cells and deliver precise treatments to tumors that are physiologically difficult to treat. At Cleveland Clinic, nanotechnology delivery systems are being tested for use in metastatic testicular cancer in addition to trying to understand their overall role in inhibiting tumor progression and tumor metastasis.

In cancer medicine, science is linked to clinical care. Nowhere is this more evident than in the field of personalized medicine. As we uncover more information about cancer cells, we are able to create tailored treatment plans that give our patients the best chance to beat their disease. We feature several stories about how we have used this approach in a variety of cancers including breast cancer, mesothelioma and uveal melanoma.

We are also pleased to introduce you to our newest staff members who bring their own unique talents and research acumen to our team.

I hope that you find the information in this publication useful in your practice. Please do not hesitate to contact me with any questions, concerns or suggestions at 216.444.6922 or bolwelb@ccf.org.

Sincerely,

Brian J. Bolwell, MD
Chairman, Taussig Cancer Institute

Mesothelioma Center Combines Expertise to Treat Rare Cancer

Uncommon and misunderstood by both patients and healthcare professionals, pleural mesothelioma is a tenacious cancer with a poor prognosis if left untreated. There are, however, effective therapeutic approaches available for this malignancy.

At Cleveland Clinic, a team of experts focuses on improving the prognosis and quality of life for patients with pleural mesothelioma through innovative treatments and research in a new multidisciplinary outpatient clinic housed at Taussig Cancer Institute.

The Multidisciplinary Pleural Mesothelioma Center draws on Cleveland Clinic’s deep expertise in medical and radiation oncology, pulmonary medicine, and thoracic surgery and uses a tumor board approach. Experts in pathology and palliative care are also part of the team.

The Disease

Mesothelioma is primarily associated with prior workplace asbestos exposure and originates in the pleura in the majority of patients. It is not lung cancer, nor is it associated with cigarette smoking.

Mesothelioma can be difficult to diagnose as the symptoms may develop slowly and initial attempts

(continued on page 4)

“This disease is not optimally treated using a single modality. That’s why we’ve assembled this team approach.”

David Mason, MD, Thoracic and Cardiovascular Surgery, Sydell and Arnold Miller Family Heart & Vascular Institute (second from right)
Mesothelioma Center Combines Expertise to Treat Rare Cancer ....2

Telemedicine Program Aims to Optimize Radiation Oncology Outcomes Internationally ....6

The Era of Personalized Medicine: Single-Dose Intraoperative Radiation Therapy for Breast Cancer ....8

Clinical Trials ....10

Nanotechnology: Small Molecules Make Huge Impact on Cancer Medicine ....12

Blood Biomarkers to Guide Surveillance and Treatment of Uveal Melanoma ....17

New Staff ....18

Highlights from the American Society for Clinical Oncology Annual Meeting ....20

Selected Publications....23
at diagnosis through sampling of pleural fluid may be negative. A diagnosis of mesothelioma can often take months to achieve, despite multiple physician visits, scans and procedures. Repeat pathologic reviews are sometimes necessary because mesothelioma can often be mistaken for other cancers histologically.

Most patients are males over the age of 60; however, family members of workers exposed to asbestos may also develop the disease through secondary exposure to asbestos fibers. Chest radiation for cancer during childhood or young adulthood is also a risk factor for developing mesothelioma later in life.

“The typical mesothelioma patient is one who had occupational exposure several decades ago, over a prolonged duration,” says James Stevenson, MD, the organizer of the center and a staff member in Solid Tumor Oncology. “They have worked in construction/HVAC, mining, welding, auto repair or other industrial occupations where fireproofing is used. We also see shipyard workers and Navy veterans, especially those who worked in engine rooms.”

The center streamlines and shortens the time to diagnosis. Doctors from multiple specialties perform an initial evaluation in a single visit at Taussig Cancer Institute. Patients diagnosed at another center will have their biopsies reviewed and confirmed by a Cleveland Clinic pathologist with expertise in mesothelioma and other thoracic cancers.

**Treatments and Clinical Trials**

Contrary to some of the myths regarding mesothelioma, a number of treatment approaches are available. Treatment options to prolong and improve the quality of life for patients include surgery, radiation and chemotherapy. Prolonged remissions can sometimes be achieved. Treatment decisions are individualized and based on a thorough understanding of each patient, his or her health and fitness level and a comprehensive assessment of the extent of their disease. Relief of mesothelioma-related symptoms, including shortness of breath and pain, is also a primary goal of the team at consultation.

David Mason, MD, Staff Surgeon in Thoracic and Cardiovascular Surgery in the Sydell and Arnold Miller Family Heart & Vascular Institute, says that the surgical treatment of pleural mesothelioma is currently evolving.

“It’s a relatively rare disease,” he says.

“Determining the right treatment for each patient is difficult and all cases require input from multiple specialists.”

Dr. Mason is an expert in radical resection of mesothelioma, which includes extrapleural pneumonectomy (removal of the lung and lining of the chest), and in lung-sparing surgical approaches that can extend and improve the lives of patients. He says that extrapleural pneumonectomy is an aggressive surgical approach that is typically used in early stages of mesothelioma and may provide the best possible outcomes.

Dr. Mason is one of only a small number of thoracic surgeons in the U.S. with expertise in performing radical resection of mesothelioma.

Pleurectomy is a lung-sparing surgery that involves complete removal of the diseased pleura without lung resection. Intraoperative hyperthermic lavage is performed as part of this procedure to treat any residual microscopic cancer.

“Our patients experience a very low rate of operative complications in these cases, due to the expertise of our center, and our comprehensive approach to treatment,” Dr. Mason adds.
The experienced multidisciplinary team decides which surgical approach is most appropriate for patients and always involves the patient and his or her family in the decision-making process.

“This disease is not optimally treated using a single modality,” says Dr. Mason. “That’s why we’ve assembled this team approach.”

Gregory Videtic, MD, a staff member in the Department of Radiation Oncology with expertise in thoracic diseases, says that the care team for these patients works together from the beginning to ensure that treatment is tailored to each situation. Dr. Videtic meets with patients at their first visit to the center even though radiation may not be part of their immediate therapy.

For the patients who are fit and have disease limited to the chest, their comprehensive program will often include radiation after surgery, because there is still a high risk that mesothelioma will recur. “Treatment is complicated and demanding,” Dr. Videtic says. “Just as the surgery is highly specialized, the radiation after resection demands great expertise and is not something we recommend be done anywhere but Cleveland Clinic — we do everything as a team here.”

Chemotherapy is also an important component of treatment and is offered to most patients as the primary form of therapy or in combination with surgery and radiation treatments. It is delivered by specialized pharmacists and nurses who keep patients informed of the treatments and their potential side effects. Pain management is also provided as appropriate.

“We use radiation therapy tailored to the patient’s needs to relieve symptoms,” says Dr. Videtic. “Effective treatment might only require a few days of therapy.”

Symptomatic care is also the focus of Palliative Medicine physicians and nurses, who are available to see and care for patients during their treatments or visits with other specialists.

The Future

Coordinated scientific and clinical research is the key to making progress against mesothelioma. Clinical trials of promising new drugs as treatments for mesothelioma are now available at Taussig Cancer Institute. (See clinical trials, page 10.)

The team also continues to explore innovative multimodal approaches for mesothelioma patients who are candidates for surgical resection.

To further aid in the battle against this complex disease, Cleveland Clinic is involved in tissue banking and genomic research and analysis in three current efforts. These involve Cleveland Clinic’s biobank, the federally funded Cancer Genome Atlas Project, as well as separate genomic profiling through a collaboration with Foundation Medicine.

Dr. Stevenson adds that the current incidence of more than 2,000 new cases per year will remain constant for at least the next decade. Asbestos still remains in use, although the substance is more highly regulated, and it still exists in many older homes and other structures.

“So, illness resulting from asbestos exposure will not completely go away,” he says. “And we know that in most cases patients will experience occupational exposure to asbestos decades before they are diagnosed with cancer.”

“We use radiation therapy tailored to the patient’s needs to relieve symptoms.”

Gregory Videtic, MD, Radiation Oncology, Taussig Cancer Institute
The African Radiation Oncology Network (Afro-NET) program strives to overcome inequalities in access to radiation therapy care and equipment across Africa’s varied geography and national borders. During the first two telemedicine collaborations in February and March 2013, clinicians from Cleveland Clinic, Canada and Africa successfully came together online to confer on complicated cases. This successful approach is the vision of the International Atomic Energy Agency (IAEA) of Vienna, Austria.

“This is an exciting collaborative effort that has far-reaching benefits for all involved,” says May Abdel-Wahab, MD, PhD, Section Head of Gastrointestinal Radiation Oncology at Cleveland Clinic. “We share cases, scans and patient histories and discuss ways to treat the patients.”

Dr. Abdel-Wahab is a consultant on the project, was a speaker at the IAEA meeting that launched the initiative and now participates in the monthly telemedicine outreach.

“The first two collaborations generated great feedback, insight and even some lessons learned,” she says. “This is a truly international tumor board.”

Evidence-based medicine backs the specific expert recommendations that are made during the teleconference. Collaborators scrupulously protect patient confidentiality at all times; a patient code replaces names on all clinical records, scans and management plans.

Treatment centers in nine of 54 African countries participate in AfroNET: Egypt, Ethiopia, Ghana, Namibia, Nigeria, South Africa (three sites), Sudan, Uganda and Zimbabwe.

Radiation oncology resources vary a great deal among the different centers. Therefore, Dr. Abdel-Wahab says that reality requires the participants to be creative, flexible and innovative in their approach to each case.

“No only do we discuss patient management, but the technical considerations for radiation therapy at the local level,” Dr. Abdel-Wahab adds.

Recognizing an invaluable educational component, Cleveland Clinic requires that radiation oncology trainees participate in the AfroNET program. “This is good experience for a radiation oncology resident,” Dr. Abdel-Wahab says. “So far they are impressed with the types of cases presented — they see a wide spectrum of cancer diagnoses, medical confounding factors and in some cases advanced-stage cancers.”

Adobe® Connect™ software facilitates the online collaboration and allows participants to see and hear each other. Dr. Abdel-Wahab says the ease of communication and the coordination among colleagues from different countries and across multiple time zones is very impressive.

The program holds a lot of potential. “There is always more to learn from challenging cases

For more information, contact Dr. Abdel-Wahab at 216.445.7930 or wahabm@ccf.org.
and difficult scenarios.” In the future, radiation oncology subspecialists at Cleveland Clinic and elsewhere may be called to share expertise on specific cancer types. In addition, the unique expertise that African colleagues bring in terms of interesting patient cases and alternative treatment approaches is valuable to the resident global health experience.

The IAEA is not only assessing the radiation oncology capabilities in centers worldwide (Egypt and South Africa, for example, already feature advanced training, treatments and equipment), but is devising solutions to aid clinicians and patients where the need remains greatest. Future plans include providing expertise and training to developing programs, and adding radiotherapy machines and brachytherapy devices, and supplying aid in establishing new centers.

The AfroNET project is initially slated to last three years. A database will be maintained and outcomes formally evaluated to determine the project’s effectiveness.

Cancer Consult provides information from Cleveland Clinic Taussig Cancer Institute specialists about innovative research and diagnostic and management techniques.

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Cleveland Clinic Taussig Cancer Institute annually serves more than 28,000 cancer patients. More than 250 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. Taussig Cancer Institute is part of Cleveland Clinic, an independent, nonprofit, multispecialty academic medical center.

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The Era of Personalized Care: Single-Dose Intraoperative Radiation Therapy for Breast Cancer

Women diagnosed with certain types of early-stage breast cancer may benefit from low-kilovoltage, single-dose radiation therapy to a lumpectomy cavity at the time of surgery.

This alternative to postsurgical whole breast radiotherapy is gaining more attention nationally, as evidenced by ongoing research led by Stephen Grobmyer, MD, FACS, head of surgical oncology at Cleveland Clinic.

“This is a great example of personalizing cancer care,” Dr. Grobmyer says. “As we learn more about tumors and interactions of tumors and treatments, we have found that not all patients need all treatments.”

Over the past 10 to 15 years, studies have found that in women with early-stage breast cancer who have had lumpectomies, if the cancer returns, it generally recurs in the immediate vicinity of the original tumor. “So we are delivering radiation to the area where there’s the greatest risk,” Dr. Grobmyer says. “Radiation travels only about 1 cm with this treatment and it adds only about 30 minutes to an hour to the length of surgery.”

Promising Early Results

When used in carefully selected patients, intraoperative radiation therapy (IORT) could offer fewer side effects and a more convenient alternative to whole breast radiotherapy, which often requires treatment every day for three to five weeks. In addition, IORT with the Intrabeam® brachytherapy (IB) device is associated with considerably lower average costs than conventional whole breast external beam therapy ($1,857 vs. $9,653), according to a recently presented and published IORT study.*

The study, based on a retrospective review by Dr. Grobmyer and colleagues at University of Florida’s College of Medicine prior to Dr. Grobmyer’s appointment at Cleveland Clinic last year, included 78 patients — most with unicentric, invasive ductal carcinoma — who underwent IB treatments during a two-year period. IB was the only radiation therapy required in 81 percent of patients. At 12 months’ follow-up, there had been no local recurrences, and cosmesis was reported as good to excellent in 92 percent of patients. Longer-term follow-up and larger-scale studies are needed.

Previously, the multicenter, international TARGIT-A trial compared whole breast radiation therapy with IORT using IB. No statistical

Future research to be powered by a national registry created by Cleveland Clinic

Differences were found in rates of local recurrence between groups at four years’ follow-up, and the study confirmed the noninferiority of the IORT treatment. However, the study mostly included patients treated outside the United States; until the recent research led by Dr. Grobmyer, very little U.S.-based data were available.

Dr. Grobmyer serves as lead investigator for ongoing IORT breast cancer research at Cleveland Clinic.

Patient Selection Critical
At Cleveland Clinic, patients who are age 60 or older with early-stage, nonaggressive breast tumors scheduled for lumpectomy may be candidates for IORT with the IB device. Nationally, Dr. Grobmyer says, some centers offer IORT treatment to selected patients with breast cancer who are age 50 or older.

“IORT applies only to certain scenarios of early-stage breast cancer, and careful selection of patients is extremely important,” says Rahul Tendulkar, MD, Cleveland Clinic radiation oncologist and IORT researcher. “Because of limited data on IORT, we have fairly conservative guidelines—we want to make sure that we aren’t putting patients at higher risk of recurrence by potentially offering less-aggressive therapy.”

A multidisciplinary approach that includes close collaboration between surgeons and radiation oncologists is critical for appropriate patient selection and optimal care, Dr. Tendulkar says.

New Application of Existing Technology
The IB device has been used successfully for a number of years in a variety of settings, such as the intraoperative treatment of GI system cancers and brain tumors following resection.

Dr. Tendulkar explains: “It’s just a matter of learning more about this application for this disease state.”

Cleveland Clinic is paving the way for broader-based, multicenter IORT breast cancer research through the creation of a national registry that will include aggregate data from 25 to 30 centers across the country.

The initiative, spearheaded by Dr. Grobmyer and Cleveland Clinic breast surgeon Stephanie A. Valente, DO, will serve as a powerful tool to study safety and short- and long-term outcomes, Dr. Grobmyer says. The secure, Web-based registry will likely include 500 to 600 patients or more.

“The national registry will create more meaning and power to advance our medical knowledge in this area,” Dr. Grobmyer explains. If larger-scale, longer-term studies yield favorable outcomes, he says, it’s possible that IORT with IB could become a standard of care for selected patients with breast cancer rather than something that only pioneering centers are doing.

Dr. Tendulkar adds: “This collaborative registry with other institutions is really important and useful to help us understand more about patients in whom patterns of recurrence are favorable and to whom we can continue to offer this type of treatment in the future.”

If you are interested in referring a patient to Cleveland Clinic for evaluation or your center is interested in participating in the registry, please contact Dr. Grobmyer at grobmys@ccf.org or 216.636.2843.
**BREAST**

**ECOG 3108**
Phase II Prospective Trial Correlating Progression-Free Survival with CYP2D6 Activity in Patients with Metastatic Breast Cancer Treated with Single Agent Tamoxifen

**Objective:** To correlate CYP2D6 score (0 vs. 1+2) and progression-free survival.

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**LYMPHOMA**

**ECOG 1411**
Randomized Phase II Four Arm Study In Patients 60 with Previously Untreated Mantle Cell Lymphoma of Therapy with: Arm A = Rituximab+ Bendamustine Followed by Rituximab Consolidation; Arm B = Rituximab + Bendamustine + Bortezomib Followed by Rituximab Consolidation; Arm C = Rituximab + Bendamustine Followed by Lenalidomide + Rituximab Consolidation; Arm D = Rituximab + Bendamustine + Bortezomib Followed by Lenalidomide + Rituximab Consolidation

**Objective:** To determine whether the addition of bortezomib (RBV) to an induction regimen of rituximab-bendamustine (RB) improves progression-free survival (PFS) compared with RB alone in patients ≥ 60 years of age with previously untreated mantle cell lymphoma. Also, to determine whether the addition of lenalidomide to a consolidation regimen of rituximab following an induction regimen of RB or RBV improves PFS compared with consolidation rituximab alone in this patient population.

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**GLIOBLASTOMA**

**DFCI2312**
An open-label, Phase II trial of orally administered PF-00299804 in adult patients with relapsed/recurrent glioblastoma (GBM)

**Objective:** This study has treatment arms that allow patients who have or have not received prior bevacizumab.

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**CASE4312**
Phase II study of TKI258 (Dovitinib) in patients with recurrent or progressive glioblastoma who have progressed on anti-angiogenic therapy (including anti-VEGF therapy)

**Objective:** Dovitinib targets both FGF (fibroblast growth factor) and VEGF (vascular endothelial growth factor) in this patient population for whom no active agents exist.

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At any given time, Taussig Cancer Institute has more than 100 cancer clinical trials underway on the main campus and at some Cleveland Clinic regional facilities. Here is a representative sample of trials that are currently accepting patients:
**MESOTHELIOMA**

**CALGB 30901**
Randomized Phase II study of maintenance pemetrexed vs. observation for patients with malignant pleural mesothelioma without progression after first-line chemotherapy

**Objective:** To determine if maintenance therapy with pemetrexed improves progression-free survival in patients with malignant pleural mesothelioma who have at least stable disease after completion of first-line therapy with pemetrexed plus cisplatin or carboplatin.

**MDS**

**CLGN 2912**
An open-label, randomized, Phase II, parallel, dose-ranging, multicenter study of sotatercept for the treatment of patients with anemia and low- or intermediate-1 risk myelodysplastic syndromes or nonproliferative chronic myelomonocytic leukemia (CMML)

**Objective:** To determine a safe, tolerable and effective dose of sotatercept that results in the greatest frequency of erythroid hematological improvement (H-E) in patients with anemia and low- or intermediate-1 risk MDS.

**MYELOPROLIFERATIVE NEOPLASMS**

**LILY 1Z11**
A Phase II Study of LY2784544 in Patients with Myeloproliferative Neoplasms

**Objective:** To assess the activity of LY2784544 therapy administered once daily, as measured by objective response rate in patients with the myeloproliferative neoplasms PV, ET and MF, including those who have demonstrated an intolerance of, failure of primary response to, or have demonstrated disease progression while on ruxolitinib.

**MULTIPLE MYELOMA**

**CASE 1A09**
A Phase I/II Trial of Very Low to Low Doses of Continuous Azacitidine in Combination with Standard Doses of Lenalidomide and Low-Dose Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma

**Objective:** To define the highest-tolerated low dose (HTLD and HTLD CKD for GFR < 60 mL/min and 30-59 mL/min, respectively) and safety of azacitidine given at low but increasing doses up to 50mg/m^2^ twice a week concurrently with GFR-adjusted lenalidomide and low dose dexamethasone in patients with relapsed or refractory multiple myeloma.

**MYELOFIBROSIS**

**GSI 1Z12**
A Phase II Study to Evaluate the Efficacy and Safety of GS-6624 in Adult Subjects with Primary, Post Polycythemia Vera or Post Essential Thrombocythemia Myelofibrosis

**Objective:** To evaluate the effects of GS-6624 on bone marrow fibrosis alone and in combination with stable doses of ruxolitinib in subjects with PMF and post-PV MF or post-ET MF.

**PROSTATE**

**CASE 1812**
High-Dose Stereotactic Radiation for Prostate Cancer

**Objective:** To assess treatment related gastrointestinal (GI) and genitourinary (GU) toxicity for patients who undergo SBRT for localized prostate cancer.
Nanotechnology is being used to overcome some of the drawbacks to oral and intravenous cancer therapies. Next-generation nanoparticles combine diagnostic and therapeutic applications, termed theranostics, a platform that allows for a deeper understanding of the behavior of nanoparticles in vivo.

Nanoparticles are submicroscopic particles with dimensions of approximately 100 to 300 nanometers (one billionth of one meter). “At the nanoscale, the physical, chemical and biological properties of materials differ,” says Vinod Labhasetwar, PhD, Professor, Department of Biomedical Engineering, Lerner Research Institute at Cleveland Clinic, who directs the Cancer Nanomedicine program. Exploiting these new
properties can lead to enhanced delivery methods of therapeutics in oncology and other specialties.

Delivery issues hinder the administration of many anti-cancer drugs. “Either they are toxic to normal cells, are not stable in the body or cleared quickly, or bind to unwanted tissue to cause serious organ failure,” he says. Doxorubicin, the most commonly used drug for treating breast cancer, for example, has an affinity for cardiac tissue, affecting cardiac function.

Many promising anti-cancer molecules have been discarded from further investigation because they could not be delivered efficiently. Recombinant proteins and peptides can be highly unstable, or the new drug molecules prove to be highly insoluble, resulting in poor absorption, or they may not lend themselves to a form suitable for injection.

Nanotechnology can overcome the lack of tumor selectivity and facilitate drug delivery by changing a drug’s characteristics, such as its biodistribution capabilities. Nanoparticles can deliver encapsulated substances to target tumor tissue and release them over time. In the case of doxorubicin, encapsulating it into lipid-based nanoparticles, which are modified with hydrophilic polymers, can prevent its uptake by the heart. In addition to selective cell targeting, nanoparticles can be engineered to improve a drug’s stability and bioavailability.

**Two Ways to Target Cell Types**

Targeted drug delivery can be accomplished through nanotechnology via two mechanisms. One mechanism, passive targeting, is based on a phenomenon termed the “enhanced permeability and retention effect,” the property by which nanoparticles have an enhanced affinity for tumor tissue relative to normal tissue, explains Dr. Labhasetwar. Tumor tissue is “hypervascular,” and hence injected nanoparticles can selectively extravasate in tumor tissue through its leaky vasculature. Drug concentration in tumors can be vastly greater than in other tissues, and an effective concentration can be maintained in the tumor for a prolonged period, potentially promoting tumor regression while reducing the frequency of administration. A high intratumor concentration of an anti-cancer drug is also important to thwart the development of resistance and disease relapse.
“As step one of a targeted approach to treatment, we have been able to identify a small-enough particle that can get by the blood-testis barrier.”

Edmund Sabanegh Jr., MD, Department of Urology, Glickman Urological & Kidney Institute

The second mechanism for targeting drug delivery to the tumor, called “active targeting,” is to design nanoparticles that bind specifically to receptors that are specifically overexpressed on tumor cells. Peptide- and antibody-targeted nanoparticles are examples of active targeting to improve anti-cancer drug delivery to tumors.

The ability to deliver a combination of drugs with synergistic activity is another beneficial property of nanotechnology, which again may permit lower doses of some cancer treatments. Because tumor cells are more sensitive to heat than are normal cells, nanoparticles that can generate localized heat in response to an external source of energy (such as iron oxide or gold nanoparticles exposed to a magnetic field or laser light) are being studied to enhance the efficacy of drugs and drug combinations, especially for localized cancers.

A challenge lies in demonstrating biocompatibility of novel nanomaterials to gain approval from the U.S. Food and Drug Administration. At present, more than 40 products based on nanotechnology are on the market and more than 100 are in different stages of clinical development, most of which are for cancer therapies, says Dr. Labhasetwar. “We are developing confidence that they can be used safely and effectively,” he says.

Targeting the Testis with Nanoparticles

Cleveland Clinic’s Department of Urology in the Glickman Urological & Kidney Institute, in collaboration with Dr. Labhasetwar’s laboratory, is working to develop nanoparticle delivery systems for use in metastatic testicular cancer. The laboratory of Edmund Sabanegh Jr., MD, Chair of the Department of Urology, is focusing on creating cisplatin-loaded nanoparticles for the treatment of testicular cancer in a mouse model. “The testes are considered immune-privileged sites, and the blood-testis barrier is difficult to penetrate, making it more difficult to treat conditions that affect the testis,” he says.

At present, high systemic concentrations of chemotherapeutic drugs are required to achieve sufficiently high intratesticular concentrations, increasing the risk of toxicity. Directly injecting the testis could cause trauma and disrupt the blood-testis barrier.

“As step one of a targeted approach to treatment, we have been able to identify a small-enough particle that can get by the blood-testis barrier,” says Dr. Sabanegh. “Step two is engineering a molecule that actively seeks out the testis. Because the testis binds follicle-stimulating hormone (FSH), a molecule that binds preferentially to FSH..."
would allow active targeting of the testis. The nice thing about nanoparticles is that we can engineer their size affinities and the drugs they carry."

A Better Understanding of Drug Resistance and Tumor Metastasis

Dr. Labhasetwar’s laboratory is currently exploring the characteristics of lipid changes in cancer cells, particularly their biophysical characteristics, with the goal of better understanding drug resistance, tumor progression and tumor metastasis. This includes investigating surface-engineered nanoparticles that would preferentially interact with the membrane lipids of malignant but not normal cells. “It’s a different approach than using antibodies and other targeting ligands,” he says. “We know that tumors have different lipid composition and biophysical properties than normal cells, and we have shown that the lipids of a drug-resistant cell are different than those of sensitive cells. We are working to use this knowledge to develop therapies that can overcome drug resistance."

Epigenetic changes in cells have been implicated in tumor initiation, drug resistance and tumor metastasis. Delivery of epigenetics-based therapeutics, such as DNA demethylating agents, may be more efficient using nanoparticles, and this strategy has shown promise in inhibiting tumor metastasis in animal models, says Dr. Labhasetwar.

Next-generation nanoparticles integrate an imaging component so that the effect of the drug-loaded nanoparticles can be assessed after they are delivered. Among imaging mechanisms, much research has been devoted to magnetic particles as contrast agents in magnetic resonance imaging. One example is the magnetic theranostic particle iron oxide, which can be imaged with magnetic resonance imaging. Surface modification of iron oxide nanoparticles may permit their therapeutic application along with their diagnostic capability. Similarly, gold nanoparticles are being explored.

“The idea is we’ll be able to make sure that the drug is penetrating the tumor,” says Dr. Labhasetwar. “We should also be able to monitor whether the tumor is shrinking or not. We assume that EPR is an effective targeting mechanism, but unless we see it in a clinical scenario, we won’t know how much drug is delivered.”

Another application of nanoparticles with imaging capability, particularly for optical imaging, is their use in defining the tumor periphery. Often it is difficult to distinguish the tumor periphery during the operation. By injecting an imaging agent, which accumulates in the tumor and illuminates upon exposure to light, the surgeon can visualize the true borders of the tumor.

The National Cancer Institute (NCI) of the National Institutes of Health now has a special program devoted to cancer nanomedicine; the NCI Alliance for Nanotechnology in Cancer. Cleveland Clinic’s investigators and clinicians are among the leaders in this promising translational field and potentially lifesaving new (nano)frontier.

“At present, more than 40 products based on nanotechnology are on the market and more than 100 are in different stages of clinical development, most of which are for cancer therapies.”

Vinod Labhasetwar, PhD, Biomedical Engineering, Lerner Research Institute
Several lines of evidence indicate that micro-
metastases are present in many patients with uveal
melanoma at the time of ophthalmic diagnosis.
In partnership with Arun Singh, MD, of Cole
Eye Institute, we have explored new options for
treating this challenging disease. An effective
strategy to improve survival in uveal melanoma
would be to identify patients with micrometastases
and suppress them before they progress to
macrometastases. Chromosomal aberrations
(monosomy-3 and others) and gene expression
profiling of tumors are superior to clinical and
histopathological factors in predicting metastasis.

Fine-needle aspiration biopsy of tumors at the
time of local therapy (plaque radiation), tumor
resection and enucleation are the methods applied
to obtain material for molecular prognostication.
The time from diagnosis of the primary tumor to
discovery of metastasis can range from weeks to
decades. Assessment of tumor tissue, however,
does not indicate whether tumor cells have actually
been shed or are forming metastasis, and whether
adjuvant treatment is reducing micrometastasis.

Early Biomarkers of Micrometastases Needed

The identification and validation of blood
biomarkers may permit early detection of
uveal melanoma metastasis and could allow
for adoption of effective strategies to suppress
micrometastases before they progress, thereby
improving prognosis. We are actively exploring
the utility of immune regulation factors in the
blood and other new blood biomarkers in an effort
to better define prognosis and monitor disease
progression in patients with uveal melanoma.

Detection of circulating melanoma cells is a
convenient test that may be useful for diagnosis,
risk stratification, identification of metastasis and
treatment monitoring in uveal melanoma. The
results of polymerase chain reaction-based and
immunomagnetic techniques tested to date are
controversial and cannot be interpreted reliably.

A variety of blood constituents, ranging from
melanoma-associated mRNA, vascular endothelial
growth factor, hepatocyte growth factor, epidermal
growth factor and insulin-like growth factor-1 (IGF-
1) have been implicated in the progression of uveal
melanoma and are measurable in patient serum
or in experimental models of uveal melanoma. For
various biological and technical reasons, these
biomarkers have not demonstrated to date the
sensitivity, specificity and predictive values neces-
sary to monitor metastasis in patients with uveal
melanoma.

Beta2-microglobulin (B2M) is a component of
the HLA class I molecule light chain. Like the
HLA class I heavy chain, tumor B2M expression
by immunohistochemistry has been associated
with metastasis in uveal melanoma. Because it is
non-covalently associated, B2M can circulate. We
studied 76 patients, 47 treated by plaque brachy-
therapy and 29 treated by enucleation. Thirty-three
(43 percent) of the tumors manifested mono-
somy-3. Most tumors were large, were located in
the choroid and were of mixed cell type. Blood was
Blood Biomarkers (continued)

drawn in patients without metastatic disease prior to fine-needle aspiration biopsy. Tumor chromosome 3 status was determined by fluorescence in situ hybridization. Levels of B2M, IGF-1 and insulin-like growth factor-binding protein-3 (IGFBP-3) were determined by enzyme-linked immunosorbent assays. Blood levels of IGF-1 and IGFBP-3 were not associated with tumor monosomy-3. In contrast, increases in blood B2M (p ≤ 0.02) were.

The independent association of increased blood level of B2M and tumor monosomy-3 status was confirmed in multivariable analysis. Measuring blood levels of B2M in patients with primary uveal melanoma may therefore have prognostic value and may help guide surveillance and adjuvant therapy recommendations.

Krista Dobbie, MD, comes to Cleveland Clinic from Sentara Healthcare of Virginia, where she served as medical director of palliative medicine. She earned her medical degree from The University of Toledo and completed a residency in internal medicine at Eastern Virginia Medical Center.

Holly Dushkin, MD, earned her medical degree from Temple University. She completed a residency in internal medicine at Temple University Hospital and a fellowship in hematology/medical oncology at Fox Chase Cancer Center.

Harold Goforth, MD, earned his medical degree from Wright State University and completed his adult psychiatry residency at Loyola Medical Center. He is board-certified in hospice and palliative medicine by the American Board of Neurology and Psychiatry and certified in pain medicine by the American Board of Pain Medicine. His areas of focus are pain and symptom management among advanced-stage illnesses and palliative medicine systems development.

Betty Hamilton, MD, earned her medical degree from the University of Chicago. She completed a residency in internal medicine at the Hospital of the University of Pennsylvania and a fellowship in hematology/oncology at Cleveland Clinic.

Deepa Jagadeesh, MD, MPH, earned her medical degree from the University of Mysore (India) and her master’s degree in public health from Boston University. She completed a residency in internal medicine and a fellowship in hematology/oncology at the University of Massachusetts Medical School.

Sudipto Mukherjee, MD, PhD, earned his medical degree from Calcutta University, in addition to a master’s degree in public health (epidemiology) and a doctorate in vision science from the University of Alabama at Birmingham. He completed a residency in internal medicine at William Beaumont Hospital (Royal Oak, Mich.) and a fellowship in hematology/oncology at Cleveland Clinic.

Tobenna Nwizu, MD, earned his medical degree from the University of Ibadan (Nigeria). He completed a residency in internal medicine at John H. Stroger, Jr. Hospital of Cook County in Chicago and a fellowship in hematology/oncology at University of Chicago Hospitals.

Chirag Patel, MD, earned his medical degree from Northeast Ohio Medical University. He completed a residency in physical medicine and rehabilitation at Pitt County Memorial Hospital and a fellowship in hospice and palliative care at The University of Texas MD Anderson Cancer Center.
Alok Khorana, MD, has joined Cleveland Clinic Taussig Cancer Institute as the Sondra and Stephen Hardis Chair in Oncology and Director of the Gastrointestinal Malignancies Program. He most recently served as Vice Chief, Division of Hematology/Oncology, and an associate professor of medicine and oncology at the James P. Wilmot Cancer Center, University of Rochester. His clinical and translational research focuses on predictive factors in gastrointestinal cancers and cancer-associated thrombosis.

Dr. Khorana serves on the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Panel and the ASCO Scientific Program Committee and on gastrointestinal committees of the Southwest Oncology Group and American College of Surgeons Oncology Group. Currently, he is chair of the International Society on Thrombosis and Haemostasis scientific subcommittee on hemostasis and malignancy.

“My goal is to make Cleveland Clinic’s gastrointestinal cancer program as patient-centered as possible,” says Dr. Khorana. “Patient-centeredness not only means that providers are highly accessible, it means that we provide individualized therapy, using the revolution in genomic medicine and tumor mutational analysis to provide each patient with the most effective treatments and access to cutting-edge clinical trials.”

Dr. Khorana earned his medical degree from The Maharaja Sayajirao University of Baroda (Gujarat, India). He completed both an internship and a residency in internal medicine at the University at Buffalo. He also completed a fellowship in hematology/oncology at the University of Rochester.

Mitchell R. Smith, MD, PhD, has been named Director of the Lymphoid Malignancy Program at Cleveland Clinic Taussig Cancer Institute. Dr. Smith joined Cleveland Clinic in 2012, after 19 years as Director of the Lymphoma Program at Fox Chase Cancer Center in Philadelphia.

His research has focused on developing targeted approaches to improve therapy of lymphoma and myeloma. The Leukemia and Lymphoma Society honored Dr. Smith with a Lifetime Achievement Award for his work with lymphoma.

Dr. Smith is an active member of the American Society of Clinical Oncology, the American Association for Cancer Research, the American Society of Hematology and the Eastern Cooperative Oncology Group. He also has been a member of the National Comprehensive Cancer Network guideline committees for non-Hodgkin’s lymphoma and myeloma.

“In addition to maintaining our excellent quality of care and collaborating with researchers to make targeted agents work better, my goal for the Lymphoid Malignancy Program is to enhance our clinical research efforts,” says Dr. Smith. “I plan to increase the range of available clinical trials and the number of our patients enrolling in them. My vision includes having selected trials open in our regional locations, where many patients are initially treated, while having drugs earlier in development available at main campus for patients requiring those options.”

Dr. Smith earned his medical degree and a doctorate in experimental pathology at Case Western Reserve University. He completed a fellowship in medical oncology and biomedical research at Memorial Sloan-Kettering Cancer Center.
The American Society for Clinical Oncology Annual Meeting brings together more than 25,000 oncology professionals from a broad range of specialties. The 2013 event was held May 31-June 4 in Chicago, with the theme of Building Bridges to Conquer Cancer.

Cleveland Clinic physicians and researchers made significant contributions to all facets of the meeting. Here, we recount some of the most notable contributions.
**Two Paclitaxel Schedules Shown Equivalent When Used As Adjuvant Therapy for Breast Cancer**

G. Thomas Budd, MD

Two schedules for paclitaxel as adjuvant therapy for breast cancer are equivalent on the endpoint of disease-free survival.

As part of a SWOG-coordinated trial, 3,294 patients with node-positive or high-risk node-negative operable breast cancer were randomized in a 2x2 factorial design to adriamycin/cyclophosphamide six doses every two weeks or adriamycin/cyclophosphamide weekly for 15 weeks, and paclitaxel every two weeks for six cycles or paclitaxel weekly for 12 weeks. At first interim analysis, the adriamycin/cyclophosphamide randomization was halted for futility. The trial was subsequently reopened at which time all patients received four cycles of adriamycin/cyclophosphamide, and the randomization to paclitaxel every two weeks or paclitaxel weekly continued.

“We were trying to show that weekly paclitaxel was better. We couldn’t show that; these two ways of giving paclitaxel look the same,” says G. Thomas Budd, MD, staff physician, Taussig Cancer Institute. A Cox model adjusting for the adriamycin/cyclophosphamide arms showed a hazard ratio of 1.08 for weekly paclitaxel compared with every two weeks. There was no significant interaction of the two factors. The estimated five-year progression-free survival was 82 percent for weekly paclitaxel and 81 percent for paclitaxel administered every two weeks.

The side effect profiles were different between the two paclitaxel schedules. Skin rash, allergic reaction and musculoskeletal pain occurred more frequently with paclitaxel administered every two weeks. The higher dose of paclitaxel and the use of pegfilgrastim with the every-two-week schedule may have contributed to the excess toxicity observed in this arm, says Dr. Budd.

“The bottom line is that paclitaxel can be given with either one of these schedules, but the toxicity appears to be a bit less with weekly paclitaxel,” he says.

**Two Cisplatin-Based Concurrent Chemoradiation Regimens Equivalent For Locally Advanced Head and Neck Squamous Cell Carcinoma**

Cristina P. Rodriguez, MD; David J. Adelstein, MD; Lisa A. Rybicki MS; Shlomo A. Koyfman, MD; John Greskovich, MD; Joseph Scharpf, MD; Benjamin J. Wood, MD; Brian Burkey, MD; Robert Lorenz, MD; Denise I. Ives, RN

Two cisplatin-based concurrent chemoradiation regimens produce similar outcomes with different toxicity profiles in the treatment of locally advanced head and neck squamous cell carcinoma.

In a phase III study, 69 patients with previously untreated stage III-IV, M0, locally advanced squamous cell carcinoma of the larynx, oropharynx, oral cavity or hypopharynx who received definitive radiation were randomized between concurrent chemotherapy with either cisplatin, 100 mg/m² on days 1, 22 and 43 (arm A); or cisplatin, 20 mg/m²/day, and 5-FU, 1,000 mg/m²/day (arm B), as continuous 96-hour infusions during weeks one and four.

With a median follow-up of 29.4 months, two-year estimates of recurrence-free survival (94 percent vs. 85 percent; \(P = 0.62\)), overall survival (96 percent vs. 83 percent; \(P = 0.07\)), locoregional control (100 percent vs. 97 percent; \(P = 0.94\)), distant metastatic control (94 percent vs. 91 percent; \(P = 0.86\)) and freedom from recurrence (94 percent vs. 88 percent; \(P = 0.0\)) were similar between arm A and arm B.

Patients randomized to arm A experienced more nephrotoxicity (26 percent vs. 3 percent; \(P = 0.007\)) and ototoxicity (11 percent vs. 0 percent; \(P = 0.042\)), but less grade ≥2 radiation dermatitis (43 percent
vs. 68 percent; \( P = 0.038 \)), neutropenia < 1,000/mm\(^3\) (34 percent vs. 65 percent; \( P = 0.012 \)) and unplanned hospitalization (43 percent vs. 68 percent; \( P = 0.038 \)). Tobacco use and human papillomavirus (HPV) status impacted outcomes more than the treatment regimen.

**Preop Chemotherapy Followed by Surgery and Postop CRT Is Feasible Treatment Option for Locally Advanced Esophagus Adenocarcinoma**

Michael J. McNamara, MD; Thomas W. Rice, MD; Gregory M. Videtic, MD; Kevin L. Stephans, MD; John F. Greskovich, MD; Davendra Sohal, MD, MPH; David Mason, MD; Sudish C. Murthy, MD; David J. Adelstein, MD

Induction chemotherapy, surgery and adjuvant chemoradiation therapy (CRT) is associated with excellent locoregional control of loco-regionally advanced adenocarcinoma of the esophagus and gastroesophageal junction, although projected distant metastatic control and overall survival remain poor.

Distant failure following CRT and surgery is common, which led to the design of a single-arm phase II study investigating the addition of induction chemotherapy. Sixty evaluable patients with clinical stage T3, N1 or M1a adenocarcinoma of the esophagus/gastroesophageal junction were enrolled. The induction chemotherapy regimen consisted of three courses of epirubicin, 50 mg/m\(^2\) on day one; oxaliplatin, 130 mg/m\(^2\) on day one; and fluorouracil, 200 mg/m\(^2\)/day continuous infusion for three weeks, followed by surgical resection. Adjuvant CRT consisted of two courses of cisplatin, 20 mg/m\(^2\)/day; and fluorouracil, 1,000 mg/m\(^2\)/day, as 96-hour infusions during weeks one and four of radiotherapy.

A symptomatic response was obtained in 79 percent, a clinical (ultrasound) response in 48 percent and a pathologic response in 41 percent (5 percent had a complete pathologic response). After a median follow-up of 31 months, the three-year projected locoregional control is 84 percent, distant metastatic control is 44 percent, relapse-free survival is 39 percent and overall survival is 42 percent. A symptomatic response to induction and the percentage of remaining viable tumor at surgery were the strongest predictors of distant metastatic control, relapse-free survival and overall survival.

**Maintenance Erlotinib in Progressive Non-Small-Cell Lung Cancer Not Supported**

Nathan A. Pennell, MD, PhD

Patients with progressive non-small-cell lung cancer (NSCLC) following an initial response to erlotinib derive no further benefit but accrue additional significant toxicity from continuing erlotinib in addition to chemotherapy compared with chemotherapy alone.

In this phase II study, 46 patients with progressive NSCLC that was initially responsive to erlotinib were randomized to pemetrexed or docetaxel at standard doses every three weeks for a maximum of eight cycles (arm A) or chemotherapy given with erlotinib on Days 2 to 19 of each cycle (arm B). Median progression-free survival was 5.4 months in arm A and 4.6 months in arm B, a nonsignificant difference (\( P = 0.569 \)). The median overall survival was 18.7 months in arm A and 14.7 months in arm B, which also failed to attain significance (\( P = 0.295 \)).

In an analysis restricted to the 31 patients with mutation in the epidermal growth factor receptor, there was again no significant difference in progression-free or overall survival between the two groups. The addition of erlotinib to chemotherapy increased the number of grade 3/4 adverse events from seven to 24. With a median follow-up of 29.4 months, two-year estimates of recurrence-free survival (94 percent vs. 85 percent; \( P = 0.62 \)), overall survival (96 percent vs. 83 percent; \( P = 0.07 \)), locoregional control (100 percent vs. 97 percent; \( P = 0.94 \)), distant metastatic control (94 percent vs. 91 percent; \( P = 0.86 \)) and freedom from recurrence (94 percent vs. 88 percent; \( P = 0.84 \)) were similar between arm A and arm B.

Patients randomized to arm A experienced more nephrotoxicity (26 percent vs. 3 percent; \( P = 0.007 \)) and ototoxicity (11 percent vs. 0 percent; \( P = 0.042 \)), but less grade \( \geq 2 \) radiation dermatitis (43 percent vs. 68 percent; \( P = 0.038 \)), neutropenia < 1,000/mm\(^3\) (34 percent vs. 65 percent; \( P = 0.012 \)) and unplanned hospitalization (43 percent vs. 68 percent; \( P = 0.038 \)). Tobacco use and human papillomavirus (HPV) status impacted outcomes more than did the treatment regimen.


ABSTRACTS


The cytidine analogs 5-azacytidine and decitabine, used to treat myelodysplastic syndromes (MDS), produce a molecular epigenetic effect, depletion of DNA-methyltransferase 1 (DNMT1). This action is S-phase dependent. Genetic factors that decrease the half-lives of these drugs could impact efficacy. The effect of CDA SNP A79C and gender on CDA expression, enzyme activity and drug pharmacokinetics/pharmacodynamics was examined in mice and humans, and the impact on overall survival was evaluated in 90 5-azacytidine/decitabine-treated patients with MDS and 76 cytarabine-treated patients with acute myeloid leukemia. Increased CDA expression/activity in males contributes to decreased cytidine analog half-life and likely contributes to worse outcomes with 5-azacytidine or decitabine therapy.


Lenalidomide and azacitidine each have activity in myelodysplastic syndromes (MDS) patients, where both microenvironment and cell-regulatory mechanisms contribute to disease pathogenesis. The objective of this multicenter, phase 2 expansion trial was to determine the efficacy and safety of combination therapy with azacitidine and lenalidomide in patients with higher-risk MDS. The overall response rate (per modified MDS International Working Group criteria) was 72 percent: Sixteen of the 36 enrolled patients achieved a complete response (CR), and 10 had hematologic improvement. Median CR duration was 17+ months; median overall survival was 37+ months for CR patients and 13.6 months for the entire cohort. The lenalidomide/azacitidine combination is well-tolerated and highly active in treating higher-risk MDS.


Tumor monosomy-3 is strongly associated with the development of metastatic disease. Tumor expression of human leukocyte antigen class I molecules and insulin-like growth factor (IGF)-1 receptor has also been associated with the development of metastatic disease. The relationship of blood levels of the human leukocyte antigen-class-I-associated β2 microglobulin (β2M), IGF-1, and its binding protein, IGFBP-3, with tumor monosomy-3 was evaluated. A total of 76 patients were studied; 47 underwent brachytherapy and 29 underwent enucleation. Thirty-three of the tumors manifested monosomy-3. Blood levels of IGF-1 and IGFBP-3 were not associated with tumor monosomy-3. Increases in blood β2M were associated with tumor monosomy-3. Measurement of blood levels of β2M in patients with primary uveal melanoma may have prognostic value and may help guide surveillance and adjuvant therapy recommendations.
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