Advances in Pulmonary Medicine Facilitate Cancer Diagnosis, Treatment

By Sarah Bronson

The lungs present unique challenges in cancer diagnosis and treatment—navigating a maze of bronchi to find and sample tissue that will lead to an accurate diagnosis of lung cancer, for example, or deciding whether to proceed with treatment for cancer in the presence of concomitant lung disease.

For these reasons, pulmonologists play an important role in the care of cancer patients. “We help diagnose lung cancer, diagnose and alleviate lung complications associated with cancer and cancer treatment, and optimize respiratory status so patients can undergo treatment safely,” said Rodolfo Morice, M.D., a professor in the Department of Pulmonary Medicine and chief of the Section of Interventional Pulmonology at The University of Texas MD Anderson Cancer Center.

Suspected lung cancer necessitates accurate diagnostic procedures and proper consideration of the lungs’ susceptibility to complications. And if cancer is present, lung function should, ideally, be optimized and conditions such as pleural effusions and pneumonia cured before cancer treatment begins. Sensitive, minimally invasive bronchoscopies and up-to-date management of lung disease can help ensure that cancer treatments are as effective as possible.

Bronchoscopic images show a tumor obstructing the right main bronchus (top) and the same bronchus after tumor debulking (bottom).
Increasing the diagnostic yield of bronchoscopy

Imaging modalities such as radiography often provide the first indication of lung cancer, but only by directly examining the tissue that had suspicious radiographic findings can a cancer diagnosis be made or ruled out. Techniques for sampling lung lesions and mediastinal lymph nodes vary in accuracy, reach, and invasiveness. The choice between an invasive diagnostic procedure such as mediastinoscopy and a less invasive procedure such as bronchoscopy depends on the location of the target, the size and hence the visibility of the target, and the patient’s ability to tolerate the potential complications from these procedures.

Previously, opting for a less invasive biopsy often meant sacrificing accuracy. But with the use of endobronchial ultrasonography (EBUS), “navigation” bronchoscopy, and autofluorescence bronchoscopy, sites of suspected lung cancer can be more accurately targeted without subjecting patients to open surgical biopsy or transthoracic needle biopsy and to increased risks such as pneumothorax, which occurs in up to 30% of patients who undergo transthoracic needle biopsies.

EBUS

Conventional white-light bronchoscopy illuminates only the inside of the airway and can sample lymph nodes based on their locations relative to endobronchial landmarks; the procedure has a diagnostic yield of only 30%–50%. Adding an ultrasonography probe to the end of a bronchoscope reveals the lymph nodes near the trachea and main bronchi as far as 5 cm beyond the bronchial walls, increasing the diagnostic yield to about 95%. Using the airway as a passage, EBUS can sample the high mediastinal, paratracheal, subcarinal, and hilar lymph nodes, reaching farther into the peribronchial tissues than mediastinoscopy, which cannot access the hilar lymph nodes.

Adding ultrasonography to bronchoscopy, already a relatively safe procedure, introduces little risk; EBUS is associated with the same infrequent complications and contraindications as conventional bronchoscopy.

Navigation bronchoscopy

Navigation bronchoscopy tracks and maps the bronchoscope’s position in real time within a three-dimensional rendering of the airways based on recently acquired computed tomography data. The end of a sampling catheter is equipped with an electromagnetic position sensor that disturbs a magnetic field encompassing the patient’s lungs and thus can be pinpointed within that field or, alternatively, with a sensor that emits electrical signals indicating its position. The sensor is placed at key points selected during the planning phase. Each of these points within the actual airways is then mapped to the corresponding point in the digital rendering, and the real-time view and the digital rendering are merged. Thus, physicians can navigate the bronchi using not only the immediate white-light view of the airways but also a de-
tailed map that is integrated with the computed tomography images.

Navigation bronchoscopy can go much farther into the lung than EBUS, entering not only the trachea and main-stem bronchi but also branches as peripheral as fifth-generation bronchi 2 mm wide. Navigation bronchoscopy facilitates the bronchoscopist’s ability to sample peripheral pulmonary lesions and complements the role of EBUS for sampling mediastinal and hilar lymph nodes, allowing for a complete diagnostic workup and nodal staging of lung cancer with a single intervention.

**Autofluorescence bronchoscopy**

Autofluorescence bronchoscopy uses blue light together with white light to detect changes in the airway that portend cancer, and this technique can direct biopsies of premalignant tissue and carcinoma in situ before the disease becomes evident on noninvasive imaging or with white light bronchoscopy alone.

To produce autofluorescence, a bronchoscope’s light is filtered to a wavelength of about 400–450 nm; this blue light causes normal chemical compounds in the airways to reflect largely green light and premalignant tissue to reflect largely red light. Unlike other fluorescence methods that require a photosensitizing compound, autofluorescence requires only light. Autofluorescence bronchoscopy may be most useful in patients at high risk of airway cancer and lung cancer patients who received radiation therapy for positive margins after resection.

Although adding blue light to conventional bronchoscopy increases the sensitivity of the bronchoscopy, particularly for detecting high-grade lesions, this technique may also increase the rate of false-positive findings. Because autofluorescence may reveal a large number of areas that look abnormal but may not all be malignant, another modality called narrow-band imaging often is used in conjunction with autofluorescence bronchoscopy to select the locations that are most likely to contain malignant tissue. Specific wavelengths of blue and green light that are absorbed by hemoglobin reveal hidden blood vessels; a disorganized, tortuous vasculature suggests malignancy. Lesions with suspicious vasculature in addition to abnormal fluorescence can then be biopsied.

**Managing lung conditions concomitant with cancer**

Conditions affecting the lungs—such as toxicity due to previous treatments, chronic obstructive pulmonary disease, pleural effusions, and pneumonia—can limit cancer treatment and decrease quality of life. Often, these comorbidities must be dealt with and respiratory function improved so that patients can begin or continue cancer treatment. George Eapen, M.D., an associate professor in the Department of Pulmonary Medicine, said, “We help patients feel better so that going into treatment, they have the best shot possible at a successful outcome.”

Pleural effusions, particularly those that recur after thoracentesis, can be a persistent hindrance to cancer treatment readiness. A useful method for managing recurring pleural effusions is the indwelling catheter, which is tunneled under the skin and inserted into the effusion site. The catheter keeps the space between the pleura dry and allows the formation of adhesions to seal the space, eventually preventing fluid from reaccumulating. Previously, patients with such effusions were hospitalized and treated with sclerosing agents or repeated thoracentesis; now these patients can drain the fluid at home and achieve effective symptom resolution. Allowing patients to drain their own effusions also gives them and their families a greater sense of involvement in their care. “The catheter allows patients to reestablish control over their bodies. That sense of empowerment is very important in maintaining their psychological well-being,” Dr. Eapen said.

Another lung comorbidity that commonly occurs with cancer and may hinder treatment is pneumonia, one of the top causes of death in patients with lung cancer or leukemia. Suspected pneumonia presents several diagnostic and treatment challenges: distinguishing inflammation due to a condition such as chemotherapy toxicity from a disease caused by a pathogen; deducing whether a pathogen is a virus, bacterium, or fungus; identifying within these pathogenic categories the particular strain of pneumonia, which will often be a strain that does not typically affect people without cancer; and selecting an effective treatment without subjecting the patient to side effects that may disrupt his or her cancer treatment.

An experimental technique being studied for identifying the organisms responsible for pneumonia is to perform whole-genome microarray analysis on lung cells from the affected patient (often acquired using bronchoalveolar lavage). Preclinical studies show that pathogens elicit specific host gene expression responses that can clarify the cause of pneumonia when other tests are not sufficient. There is hope that this or similar methods could prove clinically useful in the future for diagnosis of pneumonia.

In addition to treating specific comorbidities, pulmonologists help prepare patients for cancer treatment by improving the patients’ cardiopulmonary function. Some patients can improve their performance status through carefully titrated

“We can’t always cure, but we can ease patients’ concerns about suffocating and relieve their suffering.”

– Dr. Rodolfo Morice

(Continued on page 8)
New Drugs Increase Treatment Options for Patients with Imatinib-Resistant Chronic Myeloid Leukemia

By Zach Bohannan

In the past year, several new targeted drugs have been approved as second-line treatments for imatinib-resistant chronic myeloid leukemia (CML). These drugs include the second-generation tyrosine kinase inhibitor bosutinib and the third-generation tyrosine kinase inhibitor ponatinib, which may change the standard of care for CML.

CML treatment

CML is caused by the BCR-ABL fusion protein, a result of the Philadelphia chromosomal translocation. The prevalence of this protein makes CML ideal for treatment using targeted therapies. For many years now, imatinib, one of the first and most successful targeted antineoplastic agents, has been the first-line treatment for CML. “Most CML patients are diagnosed in what we call the chronic phase, which does not carry any recognizable drug-resistant mutations in BCR-ABL, so imatinib usually works very well at first,” said Jorge Cortes, M.D., a professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center.

The main goal of CML treatment is a complete cytogenetic response, meaning an absence of detectable Philadelphia translocations in the bone marrow. Many patients treated with imatinib have complete responses, but the subset of patients who do not are then moved to a second-line treatment. Thus, there is interest in developing second-line therapies for imatinib-resistant CML, and several drugs are currently under investigation or have recently been approved by the U.S. Food and Drug Administration for this purpose.

Bosutinib

Because ABL is a tyrosine kinase, most candidates for second-line CML treatment are tyrosine kinase inhibitors, which include dasatinib, bosutinib, and ponatinib. Bosutinib is among the most promising of these drugs. It is generally considered more potent than imatinib, and it can overcome several of the mutations that render CML resistant to imatinib.

The side effects of bosutinib are less severe—and most are less common—than those of some other tyrosine kinase inhibitors because bosutinib has less effect on the development of normal blood cells. For example, nilotinib, dasatinib, and several other tyrosine kinase inhibitors also inhibit growth factor receptors such as c-KIT and platelet-derived growth factor receptor. These receptors are important for the normal development of certain myeloid cell types. Bosutinib, however, does not affect these receptors as strongly as many other tyrosine kinase inhibitors and thus causes lower rates of neutropenia and thrombocytopenia than do nilotinib and dasatinib. Similarly, bosutinib causes lower rates of cardiotoxicity and pancreatitis than other second-generation tyrosine kinase inhibitors that are approved for treating imatinib-resistant CML. Conversely, some side effects might be more common with bosutinib.

This lack of significant side effects is one reason bosutinib is so attractive. However, Dr. Cortes said, “Although all tyrosine kinase inhibitors are very safe compared with most other chemotherapies, there can still be adverse events, and doctors should explain and discuss possible side effects with patients.” The primary side effect associated with bosutinib is diarrhea, which can occur in up to 80% of patients. However, this is usually minor and manageable.

Although bosutinib is superior to many other possible treatments for CML, it is not effective for all patients. For example, the T315I point mutation that can occur in the BCR-ABL gene renders CML resistant to imatinib, bosutinib, and most other tyrosine kinase inhibitors.

Ponatinib

Ponatinib is a very potent tyrosine kinase inhibitor that was specifically designed to treat the T315I point mutation while maintaining efficacy against all other known BCR-ABL mutations. Although ponatinib has many of the same side effects as other tyrosine kinase inhibitors, its ability to treat a previously intractable mutation makes it very promising. Because it is very effective against T315I-mutated BCR-ABL and in patients who have not responded to multiple other tyrosine kinase inhibitors, ponatinib was recently approved as a second-line treatment for CML patients.

New first-line therapy?

Because bosutinib shows so many benefits over other tyrosine kinase in-
hibitors, Dr. Cortes conducted some preliminary research into its use as a first-line therapy for CML. The initial research set out to determine whether bosutinib would offer a better cytogenetic and molecular response rate than imatinib. Dr. Cortes said, “We found that bosutinib and imatinib have similar cytogenetic response rates, so the primary endpoint of the study was inconclusive. However, in many of the other measures examined, such as the number of adverse events, bosutinib was superior.”

Another notable finding of that study was that bosutinib caused a complete cytogenetic response faster than imatinib did. Many studies have shown that speed of response has a major effect on long-term survival for CML patients. However, much more research, some of which is ongoing, will be needed before bosutinib can be recommended or officially adopted as the gold standard for CML treatment.

Ponatinib also is being studied as a first-line treatment. In an ongoing phase II clinical trial, Dr. Cortes and his colleagues are evaluating the drug’s effectiveness in patients with previously untreated chronic-phase CML. Laboratory data suggesting that it is difficult to induce ponatinib resistance makes ponatinib an attractive treatment option that could reduce the probability of acquiring resistance and thus improve the long-term outcome.

**Future directions and challenges**

CML patients require frequent monitoring to ensure their disease does not recur, and many patients remain in fear that their CML will return with a mutation that renders it resistant to currently available treatments. However, the recent approval of ponatinib and omacetaxine (a translation inhibitor also found to be active against CML) means that these mutations may prove to be less of a threat in the future.

One problem inherent in any CML treatment is that there is no way to determine whether a patient has been cured. Patients who achieve a complete cytogenetic response may undergo more sensitive molecular testing. A complete molecular response, defined as the absence of detectable BCR-ABL transcripts, is the best possible outcome a physician can assess for a CML patient, but there is still no way of knowing if the CML has been completely eliminated because even molecular tests have a limit of detection. “To completely cure CML, we need to develop other therapeutic options and better testing for residual disease,” Dr. Cortes said. “Right now, the best I can tell patients is, ‘I don’t see it (the leukemia),’ which is different from, ‘It’s gone.’” He believes that once a more powerful test is developed, tyrosine kinase inhibitors will probably need to be combined with another therapy to cure CML patients. The most likely therapy to combine with tyrosine kinase inhibition is stem cell transplantation.

However, until more powerful tests are developed, doctors will continue to treat CML as a chronic disease, which means that many patients will receive lifelong targeted therapy, whether it is imatinib or sequential treatment with multiple tyrosine kinase inhibitors as the disease mutates.

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**For More Information**

Dr. Jorge Cortes ....................713-794-5783

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**Current Treatments for Chronic Myeloid Leukemia**

**Imatinib:** tyrosine kinase inhibitor approved by the U.S. Food and Drug Administration as a first-line treatment for chronic myeloid leukemia (CML); often successful

**Dasatinib:** second-line tyrosine kinase inhibitor for some imatinib-resistant mutants

**Bosutinib:** second-line tyrosine kinase inhibitor for some imatinib-resistant mutants

**Nilotinib:** second-line tyrosine kinase inhibitor; slightly modified version of imatinib

**Omacetaxine:** alkaloid translation inhibitor for treating T315I-mutant CML

**Ponatinib:** second- or third-line tyrosine kinase inhibitor for treating T315I-mutant CML

**Stem cell transplant:** offers curative potential but with greater risks compared to therapy with tyrosine kinase inhibitors; seldom used as initial therapy but considered for patients who have not responded well to other therapies.
The Professional Oncology Education program, which was launched in 2010, provides courses for physicians and other health care professionals on various topics relating to cancer treatment. There is no charge for the courses, most of which can be taken for continuing medical education credit.

“The courses are intended to be for health care professionals at all levels and all specialties, not just oncologists,” said Kendra Woods, Ph.D., special assistant to the senior vice president in the Department of Academic Affairs. Dr. Woods works with faculty experts to develop the curriculum for each course. Some courses provide an overview of an area of cancer care, while others offer more specialized content. Most course transcripts have been translated into Spanish, French, Portuguese, Mandarin, Japanese, and Arabic.

Dr. Woods said many of the courses are designed to address topics about which little information is available to the medical community. For example, the cancer survivorship series is intended to help bridge the continuum of care between cancer hospitals and community physicians for long-term cancer survivors. “We want to empower physicians so that they’re comfortable answering their patients’ questions,” Dr. Woods said. The series includes general courses on survivorship and specific courses on the treatment of breast, prostate, and colorectal cancer survivors. The survivorship courses were among the first offered by the program, which currently includes 14 courses.

Other course topics include hereditary breast and ovarian cancer, tobacco cessation, introduction to clinical oncology, and breast cancer. Because MD Anderson has the world’s first multidisciplinary clinic dedicated to treating and studying inflammatory breast cancer, a course was developed to share lessons learned in this clinic about the diagnosis and treatment of this uncommon and difficult-to-recognize subtype.

Most of the content to date is presented in lectures, but Dr. Woods said she and her colleagues are developing courses that include case studies, chart reviews, or virtual or standardized patient scenarios. “We want to make the program more interactive,” she said. “And we act on inquiries and suggestions we receive about adding courses on specific topics.”

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• Visit www.mdanderson.org/poe
• Visit www.facebook.com/MDAndersonOncology/Resources/healthcareprofessionals
• Follow on Twitter: @MDAnderson_POE

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Dr. Ellen Manzullo, a professor in the Department of General Internal Medicine, delivers a lecture on cancer-related fatigue for the Professional Oncology Education Program.
Managing the Financial Burden of Long-Term Illness

Help is available for many patients

The cost of treatment for cancer and other diseases that require long-term care can be high, and many people with such diseases will experience some financial burden. Fortunately, resources are available to help patients and their families plan for and manage these financial challenges.

Irene Korcz, Ph.D., L.C.S.W., a senior social work counselor in the Department of Social Work at The University of Texas MD Anderson Cancer Center, has seen firsthand how treatment costs can siphon off people's savings. “Long-term illness has a big impact on a person’s finances. Many patients’ insurance plans will pay for 80% of their treatment costs, but that remaining 20% can add up quickly and be quite expensive,” she said. “And out-of-pocket costs can add up, too.”

Have a plan

If you or a family member is facing long-term treatment, it’s important to know what that treatment will cost. Talk to your doctor about the expected costs of treatment, including laboratory tests, imaging studies, clinical visits, medicines, and in- and outpatient procedures. If your doctor does not know this information, he or she may be able to refer you to someone who does. Be sure to consider out-of-pocket expenses such as child care during treatment and transportation to and from the hospital.

It is also important to know how you will pay for your treatments. Review your health insurance policy carefully to find out which costs your insurance will cover and which ones you will have to pay. Be sure you know the amounts of your copayments and deductible. You should also review your income, assets, and expenses so you can make adjustments and plan accordingly.

Some of the money you spend on medical care for yourself and your family may be deductible from your federal income tax. See Internal Revenue Service Publication 502, Medical and Dental Expenses (www.irs.gov/pub/irs-pdf/p502.pdf), for details, but remember that tax codes are subject to change.

Know your options

A social worker can be a valuable member of your support team. The hospital where you are being treated may have social workers on staff; if not, you may be able to find a social worker in your area through a service such as www.healthgrades.com. In addition to helping you manage the psychological and social aspects of your diagnosis, a social worker can help you locate sources of financial support. For example, Dr. Korcz said, “At MD Anderson, we do a financial assessment to find out what the person’s needs and financial concerns are. Based on our assessment, we try to direct him or her to the correct resources.”

Here are just a few organizations and programs whose support may be available to you.

- **Government benefit and assistance programs** provide financial or other aid to specific groups of people. For example, Medicare provides health insurance not only for people age 65 years and older but also people younger than 65 years who have certain disabilities or end-stage renal disease (a chronic illness). Medicaid provides insurance for individuals and families with low income. Social Security programs provide disability insurance benefits and other forms of financial support. To find these and other government benefit and assistance programs that you may qualify for, visit www.benefits.gov or call 800-333-4636.

- **Nonprofit organizations** provide many helpful services—support groups, counseling, and publications, for example. Some organizations also provide financial support to those who qualify. Groups that can help you locate the services of nonprofit organizations that fit your needs include the Cancer Financial Assistance Coalition (www.cancerfac.org) and Patient Advocate Foundation (www.patientadvocate.org, 800-532-5274).

- **Prescription assistance programs**, which are usually supported by pharmaceutical companies, supply medicines for free or at a reduced cost to patients who qualify. Some organizations that can help you locate prescription assistance are the Partnership for Prescription Assistance (www.pparx.org, 888-477-2669), RxAssist (www.rxassist.org), and NeedyMeds (www.needymeds.org).

Additional options for help may become available to you as your financial needs change. Talking with your social worker on a regular basis can be the key to getting the support you need.

Enlist help

Finally, it is important to have a good support system in place. Managing the financial burden and other aspects of a long-term disease can be stressful; having people to whom you can turn for support can reduce this stress.

“The main thing is to get support for yourself,” Dr. Korcz said. “It’s always good to find a supportive presence in your life—family members, friends, your doctor, or clergy, for example—to help you during your illness.”

— J. Munch

**FOR MORE INFORMATION**

- **Talk to your physician**
- **Visit www.mdanderson.org/socialwork**
- **Call askMDAnderson at 877-632-6789**
- **Visit the American Cancer Society at www.cancer.org/treatment/findingandpayingfortreatment**
- **Visit the American Association for Cancer Research at www.aacr.org/home/survivors–advocates.aspx**
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rehabilitation, i.e., an exercise program tailored to their particular needs. These programs aim to increase patients’ cardiopulmonary functional capacity and thus their ability to tolerate treatment and their quality of life regardless of whether further treatment is planned.

Sometimes all it takes to determine that a patient with less-than-ideal lung function is ready for a tough treatment is better information. Assessments prior to surgeries such as lung resection or lobectomy have become more comprehensive in recent years, examining not just individual parts of the body but what an entire person can tolerate. Lung, heart, and muscle function can be assessed individually, but broader assessments such as exercise tests show what those systems can achieve in coordination, enabling more accurate predictions of postoperative function. And it turns out that these more accurate predictions often result in more patients receiving treatment. “Of the patients who would traditionally be deemed ineligible for surgery or other treatment on the basis of lung function alone, as many as one third are actually eligible according to the more complete assessment,” said Dr. Morice.

Patients who lack the cardiopulmonary functional capacity to endure curative treatment for their cancer still can be made more comfortable, and patients who cough up blood or struggle to breathe can be given immediate relief. Interventional procedures performed through a bronchoscope can clear the airway of tumors, characterize bleeding, and place stents to keep airways open. Dr. Eapen said that one of the most valuable services he provides is simply helping patients with obstructed airways or compressed lungs breathe well again. “We can’t always cure, but we can ease patients’ concerns about suffocating and relieve their suffering,” he said.

Pulmonary medicine has been continually gaining and refining tools to guide biopsies of lung disease, manage conditions affecting the lungs, and improve patients’ quality of life. Dr. Morice expressed the hope that pulmonologists and oncologists throughout the medical community can maintain a dialogue and share expertise and perspectives.

FOR MORE INFORMATION
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Dr. Rodolfo Morice ..................... 713-563-4257

Endobronchial ultrasonography shows a subaortic lymph node (dotted line).