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Biology, More Than Chemotherapy Timing, Drives Locoregional Recurrence in Patients Who Undergo Breast-Conserving Therapy

By Joe Munch

The management of breast cancer, like that of many cancers, often requires a little bit of everything: surgery, radiation therapy, and systemic therapy with chemotherapeutic drugs or other agents.

In patients with early-stage breast cancer, breast-conserving therapy (segmental mastectomy [lumpectomy] with whole-breast irradiation) is offered whenever feasible to preserve as much of the patient's breast tissue as possible. For decades, neoadjuvant chemotherapy has been given in selected patients to shrink tumors to a size that facilitates breast-conserving therapy. Until recently, however, no large studies had compared the long-term outcomes of patients who received chemotherapy before breast-conserving therapy with those of patients who received chemotherapy after breast-conserving therapy.

A new study from The University of Texas MD Anderson Cancer Center has found that the timing of chemotherapy does not affect the risk of locoregional

Mammograms taken before (top) and after neoadjuvant chemotherapy show a reduction in tumor size. The tumor was then removed by lumpectomy with wide surgical margins. *Reprinted with permission from Kuerer's Breast Surgical Oncology, ©McGraw-Hill 2010.*

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recurrence in patients with breast cancer undergoing breast-conserving therapy and that this risk in fact is driven by the underlying biology of the tumor. The findings underscore the importance of taking a multidisciplinary approach to treating breast cancer.

Timing chemotherapy

The study, which included nearly 3,000 women who underwent breast-conserving therapy at MD Anderson between 1987 and 2005, compared the locoregional recurrence rates of patients who underwent surgery first to those of patients who underwent chemotherapy first. Patients with inflammatory breast cancer, for whom neoadjuvant chemotherapy is the standard of care, were not included in the study.

"We found that if you grouped patients by their stage of disease at presentation, it didn't matter whether you did surgery first or gave chemotherapy first; we had similar rates of locoregional control, suggesting that breast-conserving therapy after neoadjuvant chemotherapy is a viable option in carefully selected patients," said Elizabeth Mittendorf, M.D., an assistant professor in the Department of Surgical Oncology at MD Anderson and the first author of the study's report.

The study's findings confirmed what has long been suspected among those familiar with giving chemotherapy before breast-conserving therapy in appropriately selected patients.

"I'm not sure that the results of the study will change our practice, but rather, they give us some confirmation that we should continue to feel this approach is safe and effective," said co-author Thomas Buchholz, MD, a professor in and head of the Division of Radiation Oncology. "With careful multidisciplinary coordination and appropriate selection criteria, using chemotherapy followed by lumpectomy and radiation offers patients excellent outcomes and may enable patients with larger primary tumors to avoid mastectomy."

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> **– Dr. Thomas Buchholz**

The MD Anderson approach

"At MD Anderson, our approach for a long time has been that if someone will need chemotherapy, we consider giving it first, before surgery. For example, patients with tumors larger than 5 cm and patients with disease in their lymph nodes are likely to benefit from chemotherapy first," Dr. Mittendorf said.

"MD Anderson physicians are very comfortable with giving chemotherapy in the neoadjuvant setting, but some surgeons don't have the same level of comfort with the practice as we do," Dr. Mittendorf said. "Their concern is that giving chemotherapy first may interfere with appropriate surgical management."

For example, there is some hesitancy about performing breast-conserving surgery after chemotherapy because of concerns that chemotherapy will complicate assessment of the completeness of surgery. Generally, tumors that respond to chemotherapy either shrink concentrically, becoming smaller but remaining intact, or "crumble" into several smaller tumors. When a tumor crumbles, nests of the tumor can be left behind after surgery and continue to grow and metastasize, a possibility that raises the question of how much breast volume must be removed to ensure the complete resection of the tumor.

To address this concern at MD Anderson, patients' tumors are evaluated with mammography and ultrasonography both before and after neoadjuvant chemotherapy is given. These images help guide surgery. The goal of surgery is to attain at least a 2-mm margin of normal tissue. Patients with localized disease that responds well to neoadjuvant chemotherapy—those in whom a lumpectomy can be performed with negative margins—are excellent candidates for breast-conserving therapy, whereas patients in whom lumpectomy cannot be performed with negative margins are candidates for mastectomy.

"One important aspect of our approach is that we do not routinely excise the prechemotherapy volume." Dr. Mittendorf said. "Instead, we resect any residual tumor or calcifications identified on imaging studies done after neoadjuvant chemotherapy has been completed."

Weighing the benefits

If adjuvant and neoadjuvant chemotherapy result in similar locoregional recurrence rates, what guides the selection between them?

Offering surgery first has its benefits—it facilitates detailed pathological evaluation of the tumor, and in patients anxious about having a tumor remain inside their bodies while they receive 6 months of chemotherapy, immediate surgery provides some peace of mind.

However, giving chemotherapy first offers its own set of benefits. According to Ana Gonzalez-Angulo, M.D., an associate professor in the Department of Breast Medical Oncology, the main benefit is that neoadjuvant chemotherapy increases the percentage of patients who are eligible for breast-conserving therapy.

Because chemotherapy often shrinks the tumor, women with locally advanced, unresectable breast tumors can become candidates for mastectomy, and women with tumors so large that they would require mastectomy can become candidates for breast-conserving therapy.

Another advantage is that neoadjuvant chemotherapy allows oncologists

to see in vivo whether the treatment is working. When chemotherapy is given after surgery, there is no way of assessing the tumor's response; one can only really know that the therapy did not work if the cancer has recurred.

"Using chemotherapy up front allows you to make sure you are giving the right chemotherapy drugs. Obviously, if you removed the tumor first, you would be unable to tell that," Dr. Buchholz said. "It also may decrease the chance that patients will need extensive axillary lymph node removal."

"Neoadjuvant chemotherapy is kind of like a biological test of the tumor. I can see whether the tumor is responding to different chemotherapeutic agents," Dr. Mittendorf said. "I recently had a patient whose tumor actually grew when we started paclitaxel, so we immediately converted her regimen to FAC [fluorouracil, doxorubicin, and cyclophosphamide], and the tumor shrank. If we had done her surgery first, we would have given her the standard 12 full courses of paclitaxel, which we wouldn't have known was not effective in her, followed by the FAC."

Giving chemotherapy first also enables oncologists to prepare—and prepare patients—for potential treatment challenges ahead.

"We know that patients who have no residual disease—a complete response—by the end of neoadjuvant chemotherapy at the time of surgery tend to have a great prognosis," Dr. Gonzalez-Angulo said. "On the other hand, patients who have a lot of residual disease after neoadjuvant chemotherapy are probably going to have a relapse within the next few years."

Biology-driven

The MD Anderson study of neoadjuvant chemotherapy also found that several biological factors, including presenting disease stage, tumor grade, estrogen receptor (ER) status, and the presence of lymphovascular invasion or multifocal disease, predicted locoregional recurrence.

"From these data, we concluded that in certain patients, whether or not the cancer recurs is driven primarily by the biology of the tumor and less by the timing of their chemotherapy," Dr. Mittendorf said. "In fact, it's the biology of the tumor that's driving the risk of recurrence, the risk of distant disease, and likely the risk of death."

Dr. Buchholz added, "I think in every discipline—surgery, medical oncology, radiation oncology—we now are recognizing that when we say 'breast cancer' we are combining a host of different classes of disease that vary not just by the extent of disease but by the intrinsic biology."

Many of these biological subcategories are characterized by the presence or absence of ER and/or human epidermal growth factor receptor 2 (HER2). Both of these proteins affect how a patient's disease responds to systemic therapies and radiation. For example, ER-negative tumors tend to be highly responsive to chemotherapy but do not respond to hormonal therapy, whereas ER-positive tumors tend to be less responsive to chemotherapy but very responsive to hormonal therapy.

Progesterone receptor (PR) status also plays a role. Triple-negative breast cancers (those that are negative for ER, PR, and HER2) constitute 10%–20% of breast cancers, and around 40% of patients with triple-negative breast cancer experience a recurrence within 3 years after surgery. Identifying those patients early can help doctors recruit them for clinical trials.

"We want to learn more about the different subtypes of breast cancer—what are the characteristics of cancers that make them resistant to chemotherapy?" Dr. Gonzalez-Angulo said. "Today, what I can offer a patient is participation in a clinical trial. Tomorrow, hopefully I can offer a patient participation in a clinical trial of the regimen that is most likely to be effective against that patient's tumor."

The study did not cover the time during which trastuzumab—the monoclonal antibody targeting HER2 that was approved by the U.S. Food and Drug Administration in 2005—was widely used in neoadjuvant therapy. Since its introduction, trastuzumab has greatly improved outcomes among patients with HER2-positive breast cancer. For example, patients with HER2-positive disease who received just an anthracycline or taxane before surgery had a pathological complete response rate of around 23%. The addition of trastuzumab has increased this response rate to more than 50%.

"HER2 positivity indicates a high risk for locoregional recurrence. By improving the drugs that we use and getting more complete responses, we get lower rates of locoregional recurrence," Dr. Gonzalez-Angulo said.

Team effort

"The success of giving chemotherapy followed by breast-conserving therapy requires two things: one, that you pick your patients carefully, and two, that you work together as a team," Dr. Buchholz said. Forgo one, and a physician could fail the patient.

"Breast cancers should be treated in a multidisciplinary fashion; you should talk to your colleagues before you make treatment decisions," Dr. Gonzalez-Angulo said. "We never make decisions in isolation. Nobody says, 'I'm a surgeon so I'm going to operate on her first,' or, 'I'm a medical oncologist and I'm going to give her chemotherapy first because that is what I do.'"

Dr. Mittendorf echoed Dr. Gonzalez-Angulo's sentiments. "Instead of looking at a woman with breast cancer and saying, 'I can do surgery on you, so let's go to the operating room tomorrow,' we really think about giving neoadjuvant chemotherapy as an opportunity to further interrogate the biology of the cancer." ■

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New Treatments for Acute Myelogenous Leuk

By Bryan Tutt

Acute myelogenous leukemia (AML) is an aggressive and deadly malignancy, but new treatments are being developed that may prolong remissions.

According to the American Cancer Society, AML occurs most often in people over the age of 40 years, and about 9,000 people die of AML each year in the United States. While the disease can be curable, response to therapy varies as a result of patient- and disease-related factors.

"The main problem with AML treatment is the high relapse rate," said Guillermo Garcia-Manero, M.D., a professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center. "If you take 100 AML patients, about 75 will respond to therapy, but a lot of them will lose their response."

Current standard of care

Treatment for AML typically involves an induction phase of high-dose chemotherapy followed by a consolidation phase, which may include additional chemotherapy or allogeneic stem cell transplantation.

Induction chemotherapy usually consists of two cytotoxic drugs, cytarabine (also called Ara-C) and an anthracycline (daunorubicin or idarubicin). One standard regimen is the 7+3 regimen, so called because each cycle comprises 7 days of continuous cytarabine infusion during which either anthracycline is given intravenously for the first 3 days. At MD Anderson, the standard induction therapy is the IA regimen, in which each cycle comprises 4 days of high-dose continuous cytarabine infusion with idarubicin also given for the first 3 days. Dr. Garcia-Manero said the latter regimen is preferred at MD Anderson because patients receive higher doses of the drugs early in treatment with less intensive consolidation therapy, and it is hypothesized that this results in higher remission rates.

The goal of induction therapy is to bring about a first remission. This is followed by stem cell transplantation or consolidation chemotherapy, both of which are aimed at curing the patient or prolonging remission.

"Only a minority of patients are eligible for stem cell transplantation, and these patients need to be in remission before they undergo transplantation," said Jorge Cortes, M.D., a professor in the Department of Leukemia. "We also want patients who are not eligible for transplantation to stay in remission longer."

Studies of several new drugs or new combinations of existing drugs are under way in hopes of improving the percentage of AML patients who achieve complete remissions and extending the duration of those remissions.

Experimental treatments

In a recent phase II trial, treatment-naïve AML patients received cytarabine, idarubicin, and vorinostat, an oral histone deacetylase inhibitor approved for use in the treatment of peripheral T cell lymphoma. Eighty-five percent of these patients had a complete or partial response, which is among the highest overall response rates reported in AML treatment studies.

Dr. Garcia-Manero, the trial's principal investigator, said 19 of 25 eligible patients went on to receive stem cell

Dr. Guillermo Garcia-Manero *examines [redacted], who is undergoing treatment for leukemia at MD Anderson.*

kemia May Improve Patient Outcomes

transplants. "The outcomes were exceptional for the patients who had transplants," he said, adding that the patients had long-lasting remissions.

In a phase III trial expected to begin enrolling patients at MD Anderson and other institutions later this year, patients will receive cytarabine, idarubicin, and vorinostat; cytarabine and idarubicin (IA regimen); or cytarabine and daunorubicin (7+3 regimen). Dr. Garcia-Manero said the trial will test not only the efficacy of vorinostat but also which standard induction chemotherapy regimen is most effective.

In a multinational phase III study already under way, patients with relapsed or treatment-refractory AML are receiving cytarabine plus a placebo or cytarabine plus vosaroxin, which inhibits the activity of topoisomerase II. Principal investigator Farhad Ravandi, M.D., an associate professor in the Department of Leukemia, said that phase II trials of vosaroxin showed promising results.

Vosaroxin and vorinostat are not gene-specific, which enables the drugs to be effective against a broad range of tumor types but also means the drugs do not target a specific mutation.

"There has been a significant increase in the discovery of genetic abnormalities associated with AML," Dr. Ravandi said. "For all our newly diagnosed patients, we perform pretreatment tests for a wide array of molecular aberrations."

"This sort of screening has become standard at MD Anderson and other cancer centers with large leukemia programs," Dr. Cortes said. "Although this screening is mainly done for prognostic purposes, in a few instances the results can help guide therapy."

> **"Eventually, we will have more drugs that are specific for genetic abnormalities, and we're going to need to do a panel of tests to see which patients should be treated how."**
>
> **– Dr. Jorge Cortes**

For example, Dr. Garcia-Manero said, "AML patients with core binding factor abnormalities or with acute promyelocytic leukemia [APL, a subtype of

CLINICAL TRIALS: Acute Myelogenous Leukemia

A phase II study of fludarabine, cytarabine, filgrastim, and idarubicin in newly diagnosed core binding factor–associated acute myelogenous leukemia (AML) (2007-0147). Principal investigator (PI): Gautam Borthakur, M.B.B.S. The main goal of this clinical research study is to learn whether idarubicin can be added to the combination of fludarabine, cytarabine, and filgrastim without increasing side effects. This study will also observe whether the addition of idarubicin will increase the long-term chances of patients' remaining disease free.

A phase III, randomized, controlled, double-blind, multinational clinical study of the efficacy and safety of vosaroxin and cytarabine versus placebo and cytarabine in patients with first relapsed or refractory AML (the VALOR trial) (2010-0692). PI: Farhad Ravandi, M.D. The study's primary objective is to compare overall survival data between groups of patients treated with vosaroxin plus cytarabine or with placebo plus cytarabine. The secondary objectives are to compare complete remission rates and safety and tolerability data from the two treatment groups.

Phase I/II study of sorafenib and azacitidine for the treatment of patients with refractory or relapsed acute leukemia and myelodysplastic syndrome (MDS) (2010-0511). PI: Farhad Ravandi, M.D. The goal of this study is to learn if azacitidine and sorafenib can control the disease in patients with AML or MDS.

A combination of PKC412 and azacitidine for the treatment of patients with refractory or relapsed acute leukemia and MDS (2010-0374). PI: Jorge Cortes, M.D. The goal of this study is to learn if the combination of PKC412 and azacitidine can help to control refractory or relapsed acute leukemia and MDS. The safety and best dose of the combination of the drugs will also be studied.

A phase I study of AC220 in combination with induction and consolidation chemotherapy in patients with newly diagnosed AML (2011-0041). PI: Dr. Cortes. The goal of this study is to learn the highest tolerable dose and best schedule of the combination of up to two cycles of induction chemotherapy (daunorubicin, cytarabine, and AC220) and then up to three cycles of consolidation chemotherapy (AC220 and high-dose cytarabine) that can be given to patients with AML.

Phase II study of treatment of acute promyelocytic leukemia (APL) with all-trans retinoic acid (ATRA), arsenic trioxide, and gemtuzumab ozogamicin (2010-0981). PI: Dr. Ravandi. This study examines the effectiveness of ATRA and arsenic trioxide with or without gemtuzumab ozogamicin in

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AML] have a high cure rate with specific forms of therapy and no stem cell transplant." Once these patients achieve remission, they are monitored for minimal residual disease so that further treatment can be initiated if necessary.

Dr. Ravandi described two techniques used to check for residual disease. Flow cytometry detects aberrant markers on the surface of leukemia cells, and polymerase chain reaction detects gene fusion products found in some patients with AML, such as those with core binding factor leukemias or APL. "We are one of the few U.S. centers to use flow cytometry to monitor for minimal residual disease in AML patients," Dr. Ravandi said.

While patients already are benefiting from the prognostic value of pretreatment screening, its potential to guide the choice of drugs used in AML treatment is only beginning to be realized. For example, about 25% of AML patients have mutations in the *FLT3* gene.

FLT3 is a receptor kinase found on the surface of most hematopoietic progenitor cells, and AML patients with *FLT3* gene mutations have a worse prognosis than patients without mutations, making FLT3 an attractive therapeutic target. "FLT3 inhibitors work very well, but the responses they produce in patients tend to be transient, so we're combining these with other drugs to see if we can get a more durable response," Dr. Cortes said.

A pivotal trial of the FLT3 inhibitor PKC412 in combination with conventional cytotoxic drugs was recently completed. Dr. Cortes said that if the results are similar to those of earlier trials of the drug, PKC412 will likely be approved by the U.S. Food and Drug Administration for AML treatment. Dr. Cortes was not involved with that trial, but he is the principal investigator of an ongoing trial in which patients with relapsed or refractory AML or myelodysplastic syndrome receive PKC412 with azacitidine, a hypomethylating

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patients with newly diagnosed APL. This is the first U.S. study in which APL patients are treated without traditional cytotoxic agents.

Granulocyte colony-stimulating factor (filgrastim) and plerixafor with sorafenib for AML with FLT3 mutations (2008-0501). PI: Michael Andreeff, M.D., Ph.D. The aim of this phase I study is to determine the safety of plerixafor and filgrastim in combination with sorafenib for the treatment of refractory or relapsed myeloid leukemias with mutated *FLT3* and of elderly patients with AML *FLT3* mutations who are not eligible for frontline standard therapy or who refuse to be treated with intensive chemotherapy.

A phase I study evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered AMG 900 in adult subjects with acute leukemias and related disorders (2011-0369). PI: Hagop Kantarjian, M.D. This study aims to assess the safety and tolerability of AMG 900 and to evaluate its antitumor activity in patients with acute leukemias and related disorders.

A phase IB, dose-finding study of oral panobinostat in combination with idarubicin and cytarabine induction and high-dose cytarabine-based consolidation therapy in adult patients less than or equal to 65 years old with AML (2010-0591). PI: Dr. Garcia-Manero. The goals of this study are to evaluate the safety, tolerability, pharmacokinetic characteristics, and antileukemic activity of oral panobinostat (also called LBH589) combined with standard chemotherapy (idarubicin and cytarabine) in patients with AML.

Phase I/II study of plerixafor and clofarabine in previously untreated older (≥ 60 years) patients with AML with two or more unfavorable prognostic factors for whom standard induction chemotherapy is unlikely to be of benefit (2009-0536). PI: Jan A. Burger, M.D. The goals of this study are to learn about the safety of the combination of plerixafor and clofarabine and to assess, based on patients' overall response, whether this drug combination warrants further study in previously untreated AML patients age 60 years or older with unfavorable prognostic factors.

A phase IB, open-label, multicenter, dose-escalation study of oral panobinostat administered with azacitidine in adult patients with MDS, chronic myelomonocytic leukemia, or AML (2009-0619). PI: Dr. Garcia-Manero. The objectives of this study are to evaluate the safety, pharmacokinetic characteristics, and preliminary antileukemic activity of oral panobinostat combined with azacitidine in the target patient population. ■

FOR MORE INFORMATION

Visit www.clinicaltrials.org.

Controlling Nausea and Vomiting from Chemotherapy

Several techniques can be used to prevent or reduce this side effect

Nausea and vomiting are side effects of some types of chemotherapy, but much can be done to prevent or decrease these reactions and make you more comfortable during cancer treatment.

Why nausea happens

Whether you experience these side effects depends on what type of chemotherapy you receive, since not all chemotherapy drugs cause nausea or vomiting. Other factors affecting nausea and vomiting are the dosage of the drugs, how and when they are given, whether you've experienced nausea or vomiting during previous chemotherapy, and other medical conditions not related to the chemotherapy. Nausea is more common than vomiting.

Why does chemotherapy trigger these unpleasant side effects? Chemicals released during chemotherapy can stimulate an area of the brain called the chemoreceptor trigger zone, which recognizes the chemicals as toxins. Nausea and vomiting are the body's reaction to these foreign substances.

Fighting nausea

Your physician can prescribe an antinausea (also called antiemetic) medication for preventing chemotherapy-related stomach upsets. Since acute nausea or vomiting is most likely to occur within 24 hours of receiving chemotherapy, the antinausea drugs usually are given 30–60 minutes before chemotherapy begins and may be continued at prescribed intervals for several hours or days after treatment (as delayed nausea can occur 2–5 days after treatment with certain types of chemotherapy). You may receive an additional medication if you develop nausea after your chemotherapy.

There are several other steps you can take to prevent or reduce chemotherapy-related nausea:

Eat small, frequent meals. Try to eat small meals six to eight times a day rather than having fewer, larger meals.

Avoid greasy or spicy foods or foods with strong smells. Cold and bland foods may be more appealing because they give off less bothersome odors.

Drink plenty of fluids. Aim to drink 8–10 cups of liquid per day, preferably between meals rather than with meals. Try cool beverages such as water, unsweetened fruit juices, mint tea, or carbonated beverages. Since ginger often relieves nausea, try ginger tea or ginger ale. Clear soups, flavored gelatin, popsicles, and ice chips also are recommended. If smells trigger nausea, it might help to use a straw to drink from a cup with a lid.

Between meals, eat snacks that reduce nausea. These can include dry foods such as crackers, toast, dry cereals, or bread sticks. Sucking on lemon drops, mints, or ginger candy helps many people. Tart foods such as pickles or lemons are often effective for settling queasy stomachs.

Don't eat your favorite foods when you feel nauseated. This will prevent you from later associating those foods with feeling sick to your stomach.

Cook and freeze meals before your treatment starts, or have someone else cook for you. This will prevent the cooking odors from making you feel sick. Eating in a well-ventilated area or outside also reduces food odors.

Don't lie down right after you eat. If you want to rest within 30 minutes of eating, sit or recline with your head elevated.

Determine what works for you. When is the best time for you to eat and drink? Some people feel better when they eat a little just before their chemotherapy. Others feel better when they have nothing to eat or drink before treatment. Each time you start a new cycle of chemotherapy, be sure to tell your doctor or nurse what did or didn't work the last time.

Get plenty of rest. Try to take a nap when you're feeling nauseated.

Divert yourself. It can help to focus your attention on music, favorite crafts, crossword puzzles, television, reading, jigsaw puzzles, or letter writing.

Use relaxation techniques. Meditation and deep breathing can help control nausea. A number of other mind-body interventions also have proved effective for some patients. These include self-hypnosis, progressive muscle relaxation, biofeedback, guided imagery, systematic desensitization, and acupuncture or acupressure. A member of your health care team may be able to help you decide whether to try one or more of these techniques and refer you to a trained therapist.

Don't give up. Sometimes it takes a few tries before you and your doctor find what works best for reducing your nausea. Tell your health care team if you're experiencing nausea or vomiting so they can identify the medicine or combination of medicines that is most effective for you or suggest other techniques that can make you more comfortable. Always remember that it's possible to feel better. ■

– K. Stuyck

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New Treatments for Acute Myelogenous Leukemia

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agent approved for the treatment of myelodysplastic syndrome. "The early results are encouraging," he said, "and the treatment is very well tolerated."

The results of preclinical studies of another experimental drug, AC220, indicate that it may be the most potent of the FLT3 inhibitors currently available. "We did the phase I study at MD Anderson, and the drug showed significant activity," Dr. Cortes said.

A large phase II study of single-agent AC220 has completed patient accrual. "The preliminary data indicate that more than 50% of patients respond to this therapy even if they did not respond to prior therapies," said Dr. Cortes, the principal investigator of that trial and of a phase I study of AC220 combined with cytarabine and daunorubicin.

Early trials of sorafenib, a multikinase inhibitor approved for the treatment of renal cell and hepatocellular carcinomas, demonstrated its activity against AML in patients with *FLT3* mutations, and a phase II trial combining sorafenib with azacitidine is under way with promising early results.

Another kinase inhibitor, the JAK2 inhibitor ruxolitinib, was the subject of a recent phase II trial. Although the results are still being evaluated, Dr. Ravandi said, "We saw some responses in patients whose myeloproliferative disorders had progressed to AML, so there is potential for combining ruxolitinib with other drugs for these patients. This subset of patients historically has not done well with available strategies, including stem cell transplantation."

Looking ahead

Clinical trials are helping determine which treatments are effective in which patient populations. "In some studies, patients are chosen because they have a particular mutation, but in others we are trying to see which drugs will work best in which patients," Dr. Cortes said. "Eventually, we will have more drugs that are specific for genetic abnormalities, and we're going to need to do a panel of tests to see which patients should be treated how, rather than giving the same chemotherapy regimen to everybody."

From the studies described above and from studies of several other promising treatments, data are emerging to suggest that targeted therapy is starting to benefit patients in a meaningful way.

"The diagnosis, classification, and management of AML and other leukemias are becoming very complex," Dr. Cortes said. "It is becoming more and more important for leukemia patients to have a very comprehensive workup done at a center where these treatments that can be targeted to a particular abnormality are becoming available." ■

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