Deciphering Metastatic Colorectal Carcinoma

A new test that predicts response to therapy allows some patients to avoid ineffective treatment.

By Maude Veech

Metastatic colorectal carcinoma (MCRC), the second leading cause of cancer-related death in the United States, has represented a treatment quandary. Although half a dozen therapeutic agents are available, oncologists have had no reliable markers to guide the administration of those drugs. Rather, the best results have been obtained by giving all available therapies in various combinations and sequences as (Continued on page 2)
tolerated by the patient. However, recent developments in MCRC have finally brought clinicians to the cusp of individualized therapy.

The latest step toward tailored care is the discovery of a molecular marker that predicts a lack of response or, in some cases, inferior response to monoclonal antibodies (MAbs) that inhibit the epidermal growth factor receptor (EGFR). Researchers at The University of Texas M. D. Anderson Cancer Center considered the discovery so important that earlier this year, they temporarily halted all MCRC clinical trials involving EGFR MAbs at this institution; similar amendments occurred worldwide. M. D. Anderson’s trials are expected to restart in September, after the participants have had their tumors tested for the molecular marker and, if necessary, been removed from protocols involving EGFR MAbs.

“For the first time, we have a clinically proven predictive marker for MCRC that tells us when EGFR inhibitors may not be effective,” said Cathy Eng, M.D., an associate professor in Gastrointestinal Medical Oncology and the principal investigator for many of M. D. Anderson’s MCRC trials. “EGFR MAbs have improved outcomes for many MCRC patients in recent years, but we did not understand why some patients derived no benefit. Now we have a universally accepted marker to help guide our therapy, and that is significant because we can limit unnecessary patient exposure and expense by not giving EGFR MAbs to patients whose cancers are not likely to respond.”

Consider the case of a Cancer and Leukemia Group B/Southwest Oncology Group phase III trial (CALGB/SWOG 80405). Dr. Eng describes the trial as the first “head-to-head comparison” of the EGFR inhibitor cetuximab (Erbitux) and the vascular endothelial growth factor (VEGF) inhibitor bevacizumab (Avastin) in combination with cytotoxic chemotherapy; a third arm involves both biologic therapies combined with chemotherapy. With the introduction of molecular marker testing, patients whose molecular marker status suggests they will likely not benefit from anti-EGFR therapy will be recommended to withdraw from the cetuximab-containing arms—and perhaps may be referred for another experimental trial or be treated off-protocol with a standard chemotherapy regimen.

### Greater molecular understanding

The recently identified molecular marker is a mutation of the tumor suppressor gene KRAS. Studies have reported that the KRAS mutation exists in 30%–45% of MCRCs. In MCRC with a KRAS mutation, treatment with a single-agent EGFR MAb has been shown to be no more effective than best supportive care and might even worsen outcomes.

“A study in the United Kingdom that tested panitumumab (Vectibix, a fully human EGFR MAb) versus best supportive care found that the presence of a KRAS mutation in tumors rendered single-agent panitumumab as effective as best supportive care,” said Dr. Eng, who spoke on KRAS at this year’s meeting of the American Society of Clinical Oncology. However, if the mutation was not present, panitumumab conferred an improvement in progression-free survival of 5 weeks. The importance of the KRAS mutation for therapies com-

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About 85% of patients taking epidermal growth factor receptor inhibitors develop a significant rash, which can be painful and pruritic.
bining EGFR MAbs with cytotoxic chemotherapeutic agents was further verified by the CRYSTAL trial, which compared the standard chemotherapy combination FOLFOX [folinic acid [leucovorin], 5-fluorouracil [5-FU], and irinotecan [CPT-11]] with or without cetuximab in previously untreated patients. When FOLFOX with cetuximab was given to patients with the KRAS mutation, the response rate and progression-free survival duration were inferior to those of patients whose tumors did not have the mutation.

This understanding of MCRC on the molecular level came years after the development of EGFR-targeted drugs. EGFR promotes cell division and enhances cell survival, and EGFR is overexpressed in many cancers, including those of the colon, breast, lung, prostate, brain, kidney, and ovary. EGFR MAbs inhibit cell growth and cause apoptosis.

A variety of EGFR inhibitors are effective in different types of EGFR-associated cancers, but in MCRC and several others, cetuximab has been an important advance. Cetuximab, a chimeric murine monoclonal antibody against EGFR, was developed by M. D. Anderson President John Mendelsohn, M.D., and his research colleagues in the early 1980s. After nearly 2 decades of clinical investigation, the agent was approved for the treatment of MCRC in 2004 by the U.S. Food and Drug Administration (FDA). Cetuximab is used with or without cytotoxic chemotherapy to treat relapsed or refractory MCRC.

Unfortunately, some MCRC patients receive no benefit from cetuximab or other EGFR inhibitors. For a while, it was thought that testing MCRCs for their degree of EGFR overexpression would help identify those patients who would respond to EGFR-targeted therapies; however, studies have shown that such testing does not predict response.

Lee Ellis, M.D., a professor in Surgical Oncology and Cancer Biology and chair, ad interim, of the Department of Cancer Biology, believes the reason is that all colon cancers overexpress EGFR, and a failure to detect overexpression by a test represents a failure of the test, not a lack of overexpression. As Dr. Ellis noted, “Biology is not linear—things aren’t always as you expect.”

Dr. Eng agreed. “It took several years to determine that EGFR expression as detected by immunohistochemistry had no bearing on drug efficacy,” she explained.

Avoiding unnecessary treatment

The KRAS test, though, is expected (Continued on page 4)
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to be very helpful in deciding when to use an EGFR MAb. One reason to avoid giving EGFR MAbs when a KRAS mutation is present is to avoid unnecessary side effects. “About 85% of patients using EGFR inhibitors develop a significant rash,” said Dr. Eng. While treatable with topical and oral antibiotic therapies, the rash represents a quality-of-life issue; it can be painful and pruritic and can cause a patient to be self-conscious about his or her appearance.

A more dangerous side effect to be avoided is a severe allergic reaction. This occurs rarely in most patient groups—usually less than 5% of patients are affected. But for reasons still being researched, up to 30% of patients in some Appalachian states, such as Tennessee and North Carolina, are severely allergic to EGFR MAbs. Panitumumab, a second-generation EGFR inhibitor under FDA review for use with cytotoxic chemotherapy, should reduce the chance of allergic reaction in all patients to less than 1%. Still, the rash is expected to remain a problem with panitumumab, as it occurs with all EGFR inhibitors.

The high cost of anti-EGFR therapy—about $10,000 a month—also makes it important to avoid treating patients who would derive no benefit. But perhaps most important of all, the time wasted on such therapy could be better used treating patients with therapies that have a possibility of producing a tumor response, such as FOLFOX (a combination of leucovorin, 5-FU, and oxaliplatin) with bevacizumab; FOLFIRI with bevacizumab; or investigational VEGF inhibitors.

Researchers expect the KRAS test to be approved by the FDA soon. It has been used at M. D. Anderson since January, and the National Cancer Institute recently required its use in all clinical studies in MCRC that involve EGFR MAbs.

Miles to go

Despite needing many more answers, researchers are confident that therapy for MCRC will become more effective. “Hopefully, we will increasingly be able to characterize patients for predictive or prognostic reasons by the presence or absence of molecular markers,” Dr. Eng said. “This characterization of patients’ tumors would allow truly personalized medicine rather than the handful of standardized chemotherapy regimens available until now.”

For more information, call Dr. Eng at 713-792-2828.

Beyond KRAS

In addition to the KRAS mutations, two other molecular changes have been found to have clinical application in colorectal cancer patients—predicting no response but toxicity. Stanley R. Hamilton, M.D., professor and head of M. D. Anderson’s Division of Pathology and Laboratory Medicine, says there is a toxicity marker for the oldest colorectal cancer agent, 5-fluorouracil (5-FU). A deficiency of dihydropyrimidine dehydrogenase, which catalyzes 5-FU, increases 5-FU toxicity. Similarly, the chemotherapeutic agent irinotecan (Camptosar, part of the FOLFIRI drug cocktail that also includes 5-FU and folinic acid [leucovorin]) has an FDA “black box” warning that germline UGT1A1 polymorphisms (present in Gilbert syndrome, a congenital mild liver disorder) may signal the need for lower doses of the drug because such patients are at high risk of toxicity. Research is under way to determine whether the polymorphisms have significance to tumor response as well.

A Child-Centered Anesthesia for

Four-year-old [redacted] sits in the treatment room of M. D. Anderson’s Proton Therapy Center, waiting to receive a dose of radiation to treat his medulloblastoma. Stuffed monkeys hang from the gantry attached to a nearby table, and children’s art covers the cabinet doors. A set of shelves is filled with toys and stuffed animals. At [redacted] request, “I Am a Promise” plays on the CD player, and the medical team preparing him for treatment sings along.

The people singing the loudest are Vivian H. Porche, M.D., who heads the anesthesia service at the Proton Therapy Center, and Cynthia C. Williams, C.R.N.A., M.S.N., the lead nurse anesthetist and coordinator of the anesthesia service. They created the anesthesia service and are the Proton Therapy Center’s primary pediatric anesthesia team.

Dr. Porche kisses [redacted] before setting him down on the treatment table. [redacted] sits calmly as Dr. Porche lifts his shirt, and the radiation therapists gather around while Ms. Williams connects his intravenous port. He smiles a little when they let him push a button to start the anesthesia.

Seconds later, [redacted] is asleep, and six hands reach out to steady him, get him into position for treatment, and connect the various wires that lead to the machines that will monitor his vital signs. A blanket covered with pictures of bumblebees keeps him warm.

Comfortable and anesthetized, [redacted] is ready to receive proton therapy—a precise procedure for which the patient must
Dr. Vivian H. Porche, a professor in Anesthesiology and Pain Medicine, says the Proton Therapy Center’s anesthesia service allows children of all ages to receive proton therapy.

remain perfectly positioned over long periods of time. Making young patients such as [redacted] feel comfortable and relaxed during proton therapy is no small matter. Most patients have around 30 treatments (5 days a week for 6 weeks) that can last from 30 minutes to 1 1/2 hours. A bad experience early on could make for many subsequent difficult experiences.

“We don’t want them to have bad feelings or apprehension about the Proton Therapy Center or any of the people here,” said Dr. Porche, a professor in the Department of Anesthesiology and Pain Medicine. “Even though, overall, it is not a pleasant experience, we want some aspects of it to be fun, and we try to make it as positive as we can.”

The Proton Therapy Center at M.D. Anderson is the only such center in the country that treats children of all ages, Dr. Porche said. “We don’t have an age limit,” she said. “We’ve taken care of infants as young as 7 or 8 months.”

Precision and comfort are key
Considering the many advantages of proton therapy, the policy of providing proton therapy to all children, regardless of age, is significant. The unique properties of protons allow for the precise delivery of a high dose of radiation to the target area with little collateral damage to adjacent normal tissues. Such precision is especially important in children, who are prone to such long-term effects of radiation therapy as decreased bone and soft tissue growth, hormonal deficiencies, intellectual impairment, and even second tumors.

Much planning and preparation go into the delivery of proton therapy. No matter how carefully the treatment is planned, however, its successful execution depends on being able to replicate the patient’s position exactly throughout every treatment. This means that once patients are in position, they must remain so until the treatment is completed. But how many 2-year-olds can lie perfectly still for an hour at a time? Children fidget, especially when they are nervous.

Therefore, as a general rule, children 8 years old and younger require general anesthesia to keep them still and relaxed during proton therapy treatments. That is where the pediatric anesthesia team comes in.

First, the team performs a thorough evaluation of the child before treatment begins, which includes talking to the parents about the risks and benefits of anesthesia. The next step is to make sure the child feels as secure as possible. The anesthesia team waits until the patients are asleep before attaching monitoring equipment, and parents are allowed to stay until the child falls asleep and to be with the child in the recovery room when he or she wakes up.

“We try to give the patients whatever control they can have,” Dr. Porche said. “It makes them feel like they have some say in what goes on. That’s why we let them pick a song to play. And some kids like to press the anesthetic button, so we’ll preprogram it to give a safe, initial dose, and that’s what you saw with [redacted]. It just makes the child feel important. It takes the mystery out of what’s going on and lessens some of the fear.”

Dr. Porche emphasized that anesthesia team members must have good rapport with the children, and she credits Ms. Williams with being instrumental

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A Child-Centered Approach to Anesthesia for Proton Therapy

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in creating a positive atmosphere for the patients.

“Cynthia and I have put our heart and soul into making this center the best place in the world,” Dr. Porche said. “The two of us have pictures on our bulletin board of every single child we’ve taken care of, and we regularly correspond with many of them.”

Keeping a watchful eye on safety

According to Dr. Porche, administering general anesthesia in a setting outside the hospital, such as the Proton Therapy Center, requires a combination of expertise and flexibility. “Our staff is comfortable working in a remote place with no backup, because that’s what we do,” she said, adding that several safeguards are in place, including having a recovery room where the children can be observed after treatment.

The Proton Therapy Center’s pediatric anesthetic of choice is propofol, which is used to put the children to sleep quickly and keep them asleep and breathing spontaneously. An antiemetic drug such as granisetron or ondansetron also can be given to control vomiting. The dose of propofol is determined on the basis of a child’s age, weight, general condition, and cardiovascular functioning. There is no “cookie-cutter” formula for calculating the dose, however. “It is absolutely tailored to each child’s status,” Dr. Porche said. For example, medications to treat brain tumors can increase a child’s already high metabolism, necessitating a higher dose of propofol to keep the child asleep and motionless. Conversely, if a child has increased intracranial pressure, the dose may have to be lowered.

“And certainly,” Dr. Porche added, “even in the course of treatment, we may have to modify what that child receives. For instance, right now, is being treated in the hospital for a line infection and fever. He hasn’t had any problems with anesthesia, but we’re watching him very carefully.”

Dr. Porche and Ms. Williams are planning to conduct a study of their experience thus far with propofol anesthesia. The use of propofol, particularly in children, has been associated with various adverse events, including propofol infusion syndrome (PRIS), which is characterized by severe metabolic acidosis, rhabdomyolysis, hyperkalemia, lipemia, renal failure, hepatomegaly, and cardiovascular collapse. PRIS is thought to be caused by high doses and long-term use of propofol. The syndrome is very rare in both children and adults, but it has a high mortality rate (more than 50%).

“We use a fairly high dose of propofol to put the kids to sleep,” Dr. Porche said. “What we’ve seen in the more than 70 patients that we’ve treated with proton therapy since September 2006—and we’ve given over 1,500 anesthetics—is no untoward effects. So what we’re out to start proving is that you can give some of these high amounts of propofol for 6 weeks, in small daily doses, with no untoward effects.”

A brighter future

The hope of proton therapy is that, in addition to receiving better local disease control today, the children treated with proton therapy will enjoy a better quality of life in the future. “And because of our people—the radiation therapy staff, nursing staff, and anesthesia team—more children can realize the benefits of proton therapy,” Dr. Porche said.

For more information, call Dr. Porche at 713-792-6911 or the Proton Therapy Center at 1-866-632-4782.

What we’re out to start proving is that you can give some of these high amounts of propofol for 6 weeks, in small daily doses, with no untoward effects.”

– Dr. Vivian H. Porche

Protein’s DNA-Repairing Properties Warrant Scrutiny Beyond Cancer

A protein that has been linked to the promotion of carcinogenesis may actually help protect cells from becoming malignant, according to a study recently published by M. D. Anderson researchers. The findings could have implications not only for cancer research but also for the treatment of conditions such as arthritis.

The researchers examined the role of high mobility group protein B1 (HMGB1), which binds to DNA damaged by certain carcinogens. Numerous previous studies had demonstrated HMGB1’s affinity for damaged DNA, but the effects of this binding action remained unclear; some studies suggested the binding inhibits DNA repair and thus promotes cancer development.

The M. D. Anderson researchers hypothesized instead that HMGB1 facilitates the repair of damaged DNA, and the results of their in vitro study supported that hypothesis. The experiments, performed by first author Sabine Lange, a doctoral student in the Graduate School of Biomedical Sciences, demonstrated that cell survival was much lower following DNA damage when HMGB1 was absent than when it was present. Likewise, the researchers demonstrated an increased mutation rate in DNA-damaged cells lacking HMGB1. These cells also underwent significantly less DNA repair than cells containing HMGB1.

The findings were reported in July in the Proceedings of the National Academy of Sciences.

Although HMGB1 is now shown to have DNA-repairing properties, it has also been implicated in the development of inflammation. As a result, agents that block HMGB1 are being developed for the treatment of diseases with an inflammatory component such as rheumatoid arthritis and sepsis. However, identifying HMGB1’s role in DNA repair raises

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Planning Ahead with Advance Directives

As a patient, you have the right to make your own decisions about your health care. You also have the right to expect that your decisions will be honored. But if an unexpected disease or illness prevents you from communicating, how will your doctor and loved ones know your wishes for care and treatment?

One way to make sure your wishes are followed is to prepare an advance directive. An advance directive is a written statement about the kinds of medical treatment you do or do not want if you become unable to communicate. Although they vary from state to state, there are basically three types of advance directives.

**Medical power of attorney**

When you become unable to communicate, the authority to make decisions on your behalf falls to your closest relatives, usually your spouse or, if you are unmarried or your spouse has died, your children or parents. However, you may want a particular family member or other person to make these decisions. By completing and signing a form for medical power of attorney, also known as health care proxy or durable power of attorney for health care, you can appoint someone whom you know and trust to make decisions for you if you become unable to do so. This person, referred to as your agent, has the same decision-making power as you would have: he or she may agree to or refuse medical treatment or life support on your behalf.

You can limit your agent’s decision-making authority. For example, you may say that you wish to receive certain medications or treatments. You can also say whether you want to be treated by a certain physician or at a particular hospital. Your agent is obligated to follow your guidelines. Even after you have appointed an agent, you still have the power to make decisions about your care. You can take away your agent’s authority at any time, either orally or in writing, regardless of whether you are considered competent. If you designate your spouse as your agent, his or her decision-making authority will be revoked if you get a divorce unless you state otherwise on the form.

**Living will**

A living will, also known as a directive to physicians and family or surrogates, is a legal document that describes the kinds of treatments you want if you become terminally ill. A living will does not designate a person to make health care decisions for you; instead, it gives doctors instructions for how to treat you if you cannot tell them yourself. For example, you can use a living will to let your doctor know that you do not want to receive artificial nourishment (tube feeding). A living will takes effect only when you are receiving end-of-life care.

**Limitations to medical powers of attorney and living wills**

Although medical power of attorney gives decision-making authority to one person, it does not tell that person explicitly what to do in every possible situation. Similarly, while a living will can give your doctors and loved ones an idea of what you want, it does not specify what should be done in every possible situation. One approach is to set up both medical power of attorney and a living will. This way, your agent can make decisions for you based on what you have stipulated in your living will.

**Do-not-resuscitate orders**

If you stop breathing or your heart stops, health care providers are obligated to do everything medically possible to help you. But if you feel that resuscitation would only leave you permanently incapacitated, you may choose to have a do-not-resuscitate order (DNR). A DNR is a form signed by your doctor that allows you to refuse CPR or other life-sustaining treatments if you stop breathing or your heart stops.

**Preparing advance directives**

Anyone age 18 years or older can prepare an advance directive. Advance directives do not have to be complicated legal documents—they do not even have to be written by an attorney. However, to be valid, they must comply with your state’s laws. All advance directives should be signed, witnessed, and notarized. Often, you can obtain the appropriate forms from your physician or hospital. You can also contact your state’s health department to obtain the necessary forms, or simply write your wishes down yourself. Always be sure to discuss your wishes with your family and health care providers and provide them with copies of your advance directives.

Preparing an advance directive will help you have conversations about life, health, and death from a realistic perspective. These conversations will reduce the burden of decision-making for your loved ones during difficult times.

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More information about advance directives, as well as forms for medical powers of attorney and living wills, are available through M. D. Anderson’s Department of Social Work, online at http://www.mdanderson.org/departments/socialwork.

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J. Munch

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IN BRIEF
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a fundamental question about the safety of
drugs being developed to block the
protein’s activity, said senior author Karen
Vasquez, Ph.D., an associate professor in
Carcinogenesis.

“The therapy for chronic diseases such as
arthritis involves long-term treatment,”
Dr. Vasquez said. “Our findings suggest
that loss of this protein may leave patients
more vulnerable to developing cancers.
We think that the possible long-term
effects of targeting HMGB1 warrant further
study, not only in cancer therapies
but in agents for other diseases as well.”

Metformin May Boost Complete Response
in Diabetic Breast Cancer Patients

The diabetes drug metformin may help
increase pathological complete response
rates in diabetic patients with early-stage
breast cancer who take the drug during
preoperative chemotherapy, researchers
at M. D. Anderson recently found.

The retrospective study is the first to
consider the diabetes drug as a potential
antitumor agent in breast cancer patients.

Metformin has been shown to act upon
the adenosine monophosphate kinase
pathway, a cellular energy sensor and a
potentially important pathway for the
development of cancer, explained Sao
Jiralterspong, M.D., Ph.D., an instructor
in Breast Medical Oncology.

“The other interesting aspect is that
metformin works by decreasing the
amount of insulin resistance in diabetic
patients, and insulin seems to be a growth
factor for cancer,” said Ana M. Gonzalez-
Angulo, M.D., an assistant professor in
Breast Medical Oncology who presented
the findings with Dr. Jiralterspong at the
2008 American Society of Clinical
Oncology annual meeting.

Dr. Jiralterspong, Dr. Gonzalez-Angulo,
and other M. D. Anderson researchers
identifying early-stage breast cancer
patients who received adjuvant
chemotherapy before surgery and com-
pared the outcomes of non-diabetic
patients, diabetic patients taking metfor-
min, and diabetic patients not taking
metformin. The researchers found that
the pathological complete response rate
in the diabetic breast cancer patients who
took metformin was 3 times higher than
that in diabetic patients who did not take
the drug and that metformin was an in-
dependent predictor of pathological com-
plete response in diabetic patients.

The findings are preliminary, and fur-
ther investigation of metformin is needed.

“We need to study the mechanism of
the drug. Perhaps it’s the decrease in
insulin levels, or it may be that the drug
has an antitumor effect that we need
to look at in vivo,” said Dr. Gonzalez-
Angulo. “Our next step is to conduct
comparative studies to further understand
its mechanism.” The researchers are
designing a prospective trial of metformin
therapy in preoperative patients.”