A Natural Progression: M. D. Anderson Cancer Center Promotes the Study and Integration of Complementary Therapies

by Sunni Hosemann

A patient’s son, bearing a sack of herbal supplements, asks, “Do you think this will help her? I just spent $300 on it.” His mother is being treated for cancer in a clinical trial. Afraid she may be expelled from the trial, he doesn’t want to tell the protocol nurse about his purchase.

Such questions are not uncommon, said Laura Baynham Fletcher, who directs Place...of wellness at The University of Texas M. D. Anderson Cancer Center, but they aren’t asked often enough.

“We are grateful when patients ask about complementary or alternative treatments, although sadly, they often ask after having spent a significant amount of money,” she said.

According to a recent report from the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health, use of complementary and alternative medicine by Americans has increased dramatically over the past decade, with an estimated $27 billion spent for therapies and remedies that are largely unregulated and about which scientific information is sparse.

Even more troubling, between 30% and 75% of patients with cancer use some kind of alternative or complementary therapy, but fewer than 40% of these patients share that information with their physicians. In many cases, doctors fail to ask if their patients use complementary therapies, and the patients don’t consider it important information; they assume that “natural” products cannot hurt them or interfere.

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Complementary Medicine at M. D. Anderson

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with their treatment and are therefore irrelevant to their physicians. In other cases, patients keep quiet about their use of alternative therapies because they fear disapproval or rejection by their provider or disqualification from a particular treatment or clinical trial.

Who Is Using Nonconventional Therapies and Why?

Some patients reject conventional therapy altogether and embark on truly alternative paths of treatment. Others want to try alternative therapies under the watchful eye of a cancer specialist. But most patients are simply trying to cover all their bases by seeking additional therapies that they hope will complement their conventional treatment. It isn't that they do not trust the treatment they are receiving; they just want to be sure that they are doing everything that can possibly be done.

Complementary and alternative therapies that are popular among patients with cancer include mind-body approaches (such as guided imagery), psychotherapy, and physical therapies such as yoga and tai chi. Many patients are also experimenting with dietary supplements and regimens, biopharmacologic agents such as vitamins and herbal preparations, and other biologically based agents such as melatonin, shark cartilage, and mushrooms. Of these, the NCCAM has made the study of biopharmacologic agents its first research priority to address concerns about product quality and standards and potential interactions among herbs, nutrients, and medications.

Complementary & Integrative Medicine at M. D. Anderson

Although much of the literature on the topic refers to complementary and alternative medicine, at M. D. Anderson the terms “complementary” and “integrative” are preferred, said Lorenzo Cohen, Ph.D., an associate professor in the Department of Behavioral Science and newly appointed director of M. D. Anderson's Integrative Medicine Program. “Although we study and offer many complementary therapies, we don't consider them alternative medicine. They are either good medicine or bad medicine, based on scientific study. If we find that some activity or substance is helpful, then we incorporate it among the tools we have for treating and preventing cancer. If someone were to consider it an alternative and forsake other treatment modalities known to be efficacious, that would be poor medicine and ill advised,” Dr. Cohen said.

The mainstays of conventional, or standard, cancer treatment—surgery, radiotherapy, and chemotherapy—are based on years of data and thousands of clinical trials, and toxic effects and dose tolerances are known. These therapies cannot be replaced by alternatives, said Waun Ki Hong, M.D., professor and chairman of the Department of Thoracic/Head & Neck Medical Oncology and head of the Division of Cancer Medicine at M. D. Anderson. “But we know that some patients seek additional therapy at the drug store or health food store,” said Dr. Hong, “and we are very interested in studying the contribution of complementary therapies to conventional therapies.”

Numerous studies at M. D. Anderson involve natural products and other modalities that might be labeled complementary or integrative. In some ways, this research is no different than studying any modality that has promise, but there are unique problems associated with investigating nonconventional therapies. One is that the widespread use of complementary and alternative medicine sometimes negatively affects attempts to study it. Richard Babaian, M.D., a professor of medicine in the Department of Urology, is one of the investigators for the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a national study of selenium and vitamin E as potential chemoprevention agents in prostate cancer. It has been difficult to recruit patients to participate in the trial, Dr. Babaian said, because so many people are unwilling to stop taking these supplements to become part of the control arm of the study. “Such factors may cause us never to know some of the answers, never to have a scientific basis for recommendations,” he said.

“As physicians in the 21st century, we need answers for future generations—to be able to tell them what works and what doesn’t. We should not close our minds to anything that could hold an answer, but we need to demand scientific proof,” said Dr. Babaian.

Robert Newman, Ph.D., a professor in the Department of Experimental Therapeutics and director of M. D. Anderson's Pharmaceutical Development Center, became interested in natural substances and compounds about five years ago. “It's unfortunate that we cannot get better clinical data,” he said. He believes many agents that are potentially helpful languish because it is not profitable to develop them. Dr. Newman and several other scientists and physicians at M. D. Anderson have formed the Natural Products Working Group to further the study of naturally occurring compounds by sharing ideas and experiences.

“The potential benefits to patients would be huge if we can demonstrate whether these products that they are taking actually work,” said Bharat Aggarwal, Ph.D., a professor in the Department of Bioimmunotherapy and member of the Developmental Projects in Cancer Complementary and Alternative Medicine Study Section at the National Institutes of Health. Dr. Aggarwal is also chief of the Cytokine Research Group, and his search for cytokine blockers led him to work with compounds derived from natural sources. His group has shown that curcumin (a component of the spice turmeric), capsacin (found in red peppers), resveratrol (abundant in red grapes), and a host of other foods, spices, and naturally occurring substances all suppress the transcription factor NF-kappa B, which plays an important role in many cancer-related processes. Dr. Aggarwal's group reported
Dr. Bharat Aggarwal, a professor in the Department of Bioimmunotherapy, stands next to some of the usage patents for natural compounds used in his research. Dr. Aggarwal is studying a host of compounds, derived from natural sources such as foods and spices, that suppress the transcription factor NF-kappa B.

in the September issue of Cancer Research that resveratrol is effective in preventing carcinogen-induced breast cancer formation in rats. The group has also recently completed two other studies that are pending publication, one testing the effects of curcumin in multiple myeloma in vitro and the other studying curcumin plus paclitaxel in breast cancer metastases to the lungs in mice.

John Boik, a graduate research assistant in the Department of Experimental Therapeutics, has a strong interest in the potential synergism of combinations of natural products. Boik, a former civil engineer with a master’s degree in acupuncture and oriental medicine, is the author of two books about the use of natural products in cancer treatment, Cancer and Natural Medicines (1996) and Natural Compounds in Cancer Therapy (2001).

One of the benefits of combinations, Boik said, is the potential for using smaller doses of active agents. Another is the potential for multiple targets of action. Boik’s initial pilot study may be the first of its kind on combinations of natural products. He studied 12 agents, in three sets of combinations, all of which displayed some synergism and cytotoxicity in cancer cell cultures.

Where to Go for Credible Information

Information about complementary and alternative medicine abounds, but determining its veracity is often difficult. A few years ago, The University of Texas School of Public Health, a sister institution where many M.D. Anderson faculty do collaborative work, began building a Web site to provide rigorous scientific review of the literature about complementary and alternative therapies. When that project drew to a close and its valuable information was in danger of simply fading away, Stephen P. Tomasovic, Ph.D., professor of molecular and cellular oncology and vice president for Educational Programs at M. D. Anderson, sought funding for and devoted resources to adopt and perpetuate the site as the Complementary & Integrative Medicine Educational Resources (CIMER) Web site at M. D. Anderson.

Under Dr. Tomasovic’s direction, the site has been updated, and new features are added on a regular basis. The heart of the site is a collection of scientifically derived summaries and literature reviews for many popular therapies, including herbal and other biopharmaceutical agents. The summaries, now provided in English and Spanish, include background information (such as proposed mechanism of action and toxicity information), information on the research and how it was reviewed, conclusions, and annotated bibliographies. Each summary is linked to full reports for readers who want more detailed information.

"In cases where a credible comprehensive scientific review already exists, we link to that,” said Nancy Russell, M.P.H., an assistant epidemiologist who coordinates the reviews. Russell, who has worked on the site since its creation at the School of Public Health, added, “I don’t think any of us realized at the beginning how much had been published. There were literally thousands of studies—of varying quality.”

In addition to the many reviews contained on the CIMER Web site, 34 summaries of reviews of complementary therapies from Natural Standard are being added to the site. Natural Standard is an organization founded by clinicians and researchers to provide evidence-based information about complementary and alternative therapies. A research team gathers data and expert opinions for the reviews, and validated rating scales are incorporated into comprehensive monographs that are designed to aid in clinical decision making. All of the monographs undergo blinded editorial and peer review before being included in the Natural Standard database.

The CIMER site also contains U.S. Food and Drug Administration advisories, a glossary of terms related to complementary and alternative medicine, and a “Frequently Asked Questions” section derived from years of e-mail queries. The Web site has been recognized as a source of reliable information by the U.S. Department of Health and (Continued on page 4)
New AJCC Staging System for Hepatocellular Carcinoma Reflects Patient Prognosis After Surgery

by Mariann Crapanzano

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ceduled for implementation in January 2003, a new TNM staging system for hepatocellular carcinoma (HCC) has been endorsed by the American Joint Committee on Cancer (AJCC). The new system, which will be most relevant for patients without advanced cirrhosis who are candidates for surgical resection, is the outgrowth of a multi-institutional, international study that identified independent prognostic variables—most notably, vascular invasion—in the development of the disease. Although long recognized in the staging of HCC, these variables will be pivotal in framing the new T classification. Compared with the current AJCC guidelines, the new staging system will cut in half the number of groupings under the T classification and better categorize patients by prognosis.

“This is a major advance in our understanding of the prognosis of HCC after surgery,” said Jean-Nicolas Vauthey, M.D., a professor in the Department of Surgical Oncology, chief of the Liver Service at The University of Texas M. D. Anderson Cancer Center, and key collaborator in the prognostic study. According to Dr. Vauthey, researchers evaluating patient survival after resection and the benefits of different treatments will be able to stratify study populations on the basis of the prognostic factors recognized in the new staging system, allowing a more precise and accurate assessment of the effects of treatment. Enhanced understanding of the natural history of the disease and the available treatments may help clinicians select patients for different therapies.

For the majority of patients with HCC, surgery is not an option because the underlying hepatic dysfunction has progressed too far by the time the cancer is diagnosed. In many cases, therapy for these patients is directed in part by clinical staging systems that emphasize hepatic function, such as the Okuda staging system, the Cancer of the Liver Italian Program (CLIP) score, or the Barcelona Clinic Liver Cancer (BCLC) staging system. For patients whose hepatic function is preserved, however, pathologic staging systems, such as the AJCC system, help to assess patient characteristics and guide therapy.

The T classification under the AJCC staging system currently in effect consists of 10 complex categories that are based in part on the size of the largest tumor, the number and location of tumor nodules, and the extent of vascular invasion or involvement of adjacent organs. According to Dr. Vauthey, a substantial overlap in prognosis exists between categories.

Several major hepatobiliary centers worldwide—M. D. Anderson, Mayo Clinic (Rochester, MN), Hôpital Beaujon (Paris, France), and Kyoto University Graduate School of Medicine (Kyoto, Japan)—engaged in a cooperative effort to evaluate the relationship between the 10 categories under the current T classification and prognosis. With more than 2,200 pathologic sections of HCC from 557 patients who had undergone complete resection, researchers amassed enough data to conduct an analysis that would carry substantial statistical weight.

“The strength of this study is in the number of patients and the detailed analysis,” said Dr. Vauthey.
Hepatocellular Carcinoma

The investigators performed a complete pathologic review of every specimen and multivariate analyses of outcome and survival data. What they found were distinct prognostic indicators for HCC. Perhaps the most important of these was vascular invasion. When patients were stratified into three groups by the extent of vascular invasion, significant differences in survival rates among groups emerged. The five-year survival rate for patients whose HCC showed no vascular invasion was 48%; for patients with microvascular invasion, 33%; and for patients with major vascular invasion, 14%. Tumor number and tumor size were also prognostic, although not to the extent that vascular invasion was.

These results were the foundation for the new T classification, in which extent of vascular invasion, number of tumor nodules, and size of the largest tumor each will take on a new significance. The result is a greatly simplified T classification that will stratify patients by prognostic factors. The N and M classifications will remain unchanged.

The new TNM staging system for HCC is described in detail in the sixth edition of the AJCC Cancer Staging Manual published in May 2002. The new T classification will place tumors into four main categories. T1 will comprise all solitary tumors without vascular invasion, regardless of tumor size; T2, solitary tumors with vascular invasion or multiple tumors measuring 5 cm or less; T3, multiple tumors larger than 5 cm or any tumor involving a major branch of the portal or hepatic veins; and T4, tumors that directly invade adjacent organs (other than the gallbladder) or that perforate the visceral peritoneum. (See Table, page 6.)

The classification of large tumors without vascular invasion as T1 is a major break from the current classification scheme, in which no tumors larger than 2 cm are considered to be T1. Dr. Vauthey said the multi-institutional study showed that the five-year survival rate for patients who undergo resection of a solitary HCC nodule without vascular invasion exceeds 50%, regardless of the size of the tumor.

Liver disease (fibrosis or cirrhosis) also is considered to be prognostic, said Dr. Vauthey, conferring a worse prognosis for each category of the T classification. The importance of liver disease to outcome will be recognized under the new TNM staging system: patients in each classification will be further stratified by the level of fibrosis, which is determined on a scale of 0 to 6. A fibrosis score of 0 to 4 signifies no to moderate fibrosis, whereas a fibrosis score of 5 or 6 signifies severe fibrosis or cirrhosis.

According to Thomas D. Brown, M.D., a professor in the Department of Gastrointestinal Medical Oncology and Digestive Diseases, the inclusion of liver disease as a prognostic factor represents a significant advance in the assessment of the role of therapeutic intervention in hepatic malignancies. Dr. Brown explained that anticancer therapies—even potentially curative surgery, radiation therapy, and systemic chemotherapy—are limited by the effects of underlying cirrhosis and liver dysfunction that usually accompany hepatobiliary tumors. Therefore, it is important to identify not only patients who can benefit from therapy but also those who are unlikely to benefit from, and in fact may be harmed by, therapeutic intervention, with its significant associated risks and morbidity.

"Historically," said Dr. Brown, "the normal liver tissue environment has not been taken into account when staging hepatic tumors, so this represents an expanded concept of staging, one that incorporates an assessment of liver function, not just anatomy."

The AJCC's guideline on clinical staging, which is given in connection with the description of the pathologic TNM staging, demonstrates the significance of liver disease to treatment and outcome. It states that in cases in which advanced cirrhosis directs the prognosis, the relevance of the T classification to prognosis may diminish, and other staging systems (that is, the Okuda staging system, the CLIP score, and the... (Continued on page 6)
BCLC staging system may help determine prognosis.

Yehuda Z. Patt, M.D., a professor in the Department of Gastrointestinal Medical Oncology and Digestive Diseases at M. D. Anderson, believes that the enhanced emphasis on vascular invasion and underlying liver disease in the new AJCC staging system will have the greatest impact on patients who are candidates for surgical resection, and he emphasized the continued relevance of the Okuda and BCLC staging systems and the CLIP score for patients with advanced cirrhosis who are not candidates for surgery.

"Ninety percent or more of the patients I see are not candidates for surgical intervention, in many cases because of underlying liver cirrhosis and in many cases because of vascular invasion," Dr. Patt said. "For those patients, the relevant staging system would be one that is focused substantially more on underlying liver reserve and cirrhosis. If the patient has significant cirrhosis to the degree that the remaining liver after resection would not be adequate to sustain patient survival... the size of the tumor itself becomes less relevant."

Studies have shown that underlying liver disease is also associated with the development of HCC years after the initial diagnosis and treatment. In a separate multi-institutional study using the same patient database of more than 500 patients who had undergone hepatic resection for HCC, Dr. Vauthey and his colleagues identified 145 patients who had survived five years. In this subgroup of patients, the researchers evaluated whether hepatitis and fibrosis were associated with survival longer than five years. They found that five-year survivors with a fibrosis score of 0 to 2 were unlikely to die from HCC, whereas patients with fibrosis scores of 3 to 6 had an increased mortality rate from HCC.

"We looked at all the factors—such as vascular invasion, size of tumor—and we didn't find that any tumor factor affected survival after five years, but liver disease affected survival after five years," said Dr. Vauthey. "If a patient has a normal liver [and survives five years after diagnosis and resection of HCC], the patient has a greater than 80% chance of remaining alive without recurrence of HCC beyond five years."

The ability to stratify patients with resectable HCC by the prognostic factors under the new T classification and fibrosis score will affect how researchers analyze the effects of treatment. Thus, researchers studying new treatments for HCC can better determine whether improved survival rates are the result of the treatment or simply the outcome associated with favorable prognostic factors. Dr. Brown believes that the new system may help to determine clinically which patients will or will not likely benefit from therapy.

"Any system that gives a more accurate prognosis allows us to more effectively select patients for therapy," said Dr. Brown. "It will help to ensure that patients who can benefit from therapy will receive the therapy."

For more information, contact Dr. Vauthey at (713) 792-2022 or Dr. Brown at (713) 792-7770.

1 Dr. Patt has since retired from M. D. Anderson.
Many patients travel great distances to receive care at a specialized cancer center like The University of Texas M. D. Anderson Cancer Center, often without knowing what to expect when they arrive. Being far from home in a strange city and undergoing treatment for cancer are difficult, but cancer centers have many departments and services available to make the journey and the accommodations for patients and their families as pleasant as possible.

The first step to becoming a patient at any cancer center is referral. Patients can now refer themselves to most centers or be referred by their primary care physician. When making an appointment, the patient (or his or her doctor or caregiver) must provide information about the diagnosis and any previous treatment. The M. D. Anderson New Patient Referral Office can be contacted by telephone at (713) 792-6161 or (800) 392-1611, by fax at (713) 792-2504, or via the Internet at https://www2.mdanderson.org/sapp/contact/referral.cfm (for patients) or https://www2.mdanderson.org/sapp/contact/referral.cfm (for physicians).

Large cancer centers are often able to negotiate discounts with airlines and ground transportation agencies for patients and their families. Some centers even have an on-site, full-service travel agency (at M. D. Anderson, call Patient Travel Services at [888] 848-9992).

Information about transportation and directions to a center can be obtained by calling the center or by accessing the center’s Web site.

For patients with financial needs, AirLifeLine and Angel Flight provide free air transportation to treatment facilities. Patients can find out if they qualify by calling AirLifeLine at (877) 247-5433 or Angel Flight America at (877) 621-7177 or by visiting their Web sites at www.airlifeline.org and www.angelflight.org.

Lodging

Some cancer centers offer on-site accommodations for patients and their families. The Jesse H. Jones Rotary House International Patient Hotel, which is owned by M. D. Anderson and managed by Marriott Conference Centers, is located directly across the street from M. D. Anderson and connected to the hospital by an elevated walkway. Patients who want to learn more can call the Rotary House at (800) 847-5783 or (713) 790-1600 or visit the Web site at www.mdanderson.org/departments/rotaryhouse.

Most centers also provide information about hotels and other lodging located near the center. Apartment complexes near M. D. Anderson and throughout Houston are available to patients who require long-term care and to their families. Patients can call Case Management at (713) 745-2850 or Social Work at (713) 792-6195 for more information.

Medical interpreters, business services, and even companions who run errands and serve as guides.

A concierge desk, staffed by M. D. Anderson volunteers, is located in the first-floor lobby of the Rose Zone in the hospital’s Clark Clinic. Volunteers give directions and provide patients and family members with information about transportation, housing, and restaurants. The concierge desk can be reached at (713) 794-1158.

Patients from outside the United States often require additional services. Representatives in the International Patient Center at M. D. Anderson assist patients in translating written and spoken language, finding appointments, completing forms, getting around the institution, and learning about special services. They are even available to speak with patients before they come to M. D. Anderson about such issues as which personal items and medical records to bring, financial arrangements, and transportation. Patients can call the International Patient Center at (713) 745-0450 (from Mexico, [800] 811-6167; from Venezuela, [800] 12338) and visit its Web site at www.mdanderson.org/departments/ipc.

To learn more about services at M. D. Anderson, contact the Department of Patient Advocacy and Guest Relations at (713) 792-7776 or (713) 794-4750.

For more information, contact your physician or contact the M. D. Anderson Information Line:

(800) 392-1611 within the United States, or
(713) 792-6161 in Houston and outside the United States.

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Complementary Medicine: Research, Education, and Communication

Stephen P. Tomasoic, Ph.D.
Professor of Molecular and Cellular Oncology and Vice President for Educational Programs

Many people today are seeking more holistic ways of dealing with disease and searching for complements or alternatives to current practices, and our patients at M. D. Anderson Cancer Center are no exception.

In a survey conducted more than four years ago, we discovered many of our patients were using complementary or alternative medicines while being treated by us—often without telling us. Some of the patients said that they did not disclose their use of complementary or alternative medicine because they didn’t think it was important. Others were concerned that their doctor would be angry or offended. Some didn’t divulge the information simply because they weren’t asked.

Patients have been led to believe that nutritional supplements, vitamins, and other “natural” products are not harmful. That may be true in many cases, but increased use of such products obtained from a largely unregulated industry has revealed problems: active ingredients that are not present as labeled, toxic effects from misuse, contamination, and potentially harmful interactions with conventional drugs used to treat serious medical conditions.

As awareness of these issues increases, many patients are becoming less naive about complementary or alternative approaches and are seeking authoritative information. In turn, we and other academic medical centers are trying to identify safe and helpful complementary approaches and educate our medical professionals, patients, and the public about those approaches.

M. D. Anderson has begun integrating the best complementary approaches with our conventional care. Our research efforts include determining which approaches may improve quality of life or other clinical outcomes when given in combination with conventional treatment. We provide complementary approaches known to be safe without charge through our Place... of wellness. We have also increased our efforts to educate our faculty and staff about complementary and alternative approaches and how to communicate with patients about them. We want our physicians and staff to be empathetic to patients who use or want to use complementary approaches and be able to offer them authoritative guidance about their options.

Research into folk remedies, natural products, and the approaches of other medical traditions has yielded important discoveries that have become part of allopathic medicine. Hopefully, additional advances will come from the increased focus of the medical establishment on this area. Just as important, we may be able to discard approaches of no value or potential harm and better educate everyone about the potential benefits and dangers of complementary and alternative approaches.