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REPORT TO PHYSICIANS

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Cancer Chemoprevention: A Prescription for Health?

The field of cancer chemoprevention has made rapid gains in less than two decades, but the search is still on for agents that will be both safe and effective in the long term.

By Dianne C. Witter

It's an intuitive concept and, on the face of it, a simple one: Wouldn't it be better to prevent cancer than to wait for a tumor to form and then launch an attack? That's the philosophy behind the relatively new and quickly growing field of cancer chemoprevention—using medications or natural substances to initiate a pre-emptive strike that will prevent or delay cancer, rather than taking action only after a malignancy has developed.

The idea has found a receptive audience in the medical and scientific communities and among the public. Significant research successes have been achieved, and there is strong federal support for developing chemopreventive agents: more than 100 such drugs have been or are in early clinical trials supported by the U.S. National Cancer Institute, and just as many are in preclinical studies. In fact, the National Cancer Institute has established six consortia for phase I and II clinical trials of cancer chemopreventive agents; each consortium consists of international cancer research centers led by a U.S. center. A handful of agents have earned U.S. Food and Drug Administration approval for use as chemopreventives or are showing efficacy in phase III trials.

"Chemoprevention represents a very different way for physicians to think about cancer treatment, but one that is playing an increasingly important role in medicine," said Waun Ki Hong, M.D., professor and head of the Division of Cancer Medicine at The University of Texas M. D. Anderson Cancer Center. "Cancer doesn't begin with the appearance of a tumor; by the time a tumor has formed, the processes that lead to cancer have been developing for years, often for decades. The idea behind chemoprevention is to interrupt the process before it is too firmly entrenched."

Early successes

In the early 1990s, Dr. Hong and colleagues demonstrated for the first time that cancer chemoprevention is possible in humans; they demonstrated that high-dose retinoids could stop or reverse the progression of oral precancerous growths and prevent new cancers in patients with a history of head and neck malignancies. These vitamin A analogs appear to suppress carcinogenesis through several routes, including inhibiting the growth and dif-

(Continued on page 2)

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ferentiation of premalignant and malignant cells.

The concept of chemoprevention is not new—a similar approach has been used for years to ward off heart disease. People at risk for heart attack are prescribed medications that treat hypertension and/or elevated cholesterol, significantly lowering their heart attack risk. The solutions are more complex for cancer, given its heterogeneity, but some important clinical strides have been made since Dr. Hong's vitamin A findings less than two decades ago.

The first chemopreventive agent to reach the clinic—and possibly the best known—was tamoxifen, which has been shown to cut breast cancer incidence in high-risk women by 50%. It was followed by finasteride, found to reduce prostate cancer incidence by 25% in men at high risk for the disease. However, the large-scale trials that confirmed these benefits brought to light a troublesome issue: the drugs caused serious side effects in some patients. This is an issue of particular concern when considering long-term administration of a drug to healthy people who may or may not develop cancer.

Balancing act: risks vs. benefits

"This trade-off between agent risks and benefits has led to a new focus in cancer prevention—interventions for specific groups of people who will be most likely to benefit," said Scott M. Lippman, M.D., professor in and chair of the Department of Thoracic/Head and Neck Medical Oncology and principal investigator of the phase I and II clinical trials of the cancer chemopreventive agents consortium headed by M. D. Anderson. "Subgroups of people who most likely will benefit from cancer prevention include people who are at a very high risk of developing cancer and/or at-risk individuals who have the highest potential sensitivity to an agent's beneficial effect. Efforts to identify these target subpopulations will be crucial to the future of cancer prevention."

Experience with celecoxib (Celebrex) and other COX-2 inhibitors illustrates the importance of the risk/benefit ratio in patient selection, according to Bernard Levin, M.D., professor emeritus and former vice president and head of the Division of Cancer Prevention and Population Sciences. "COX-2 inhibitors have shown impressive efficacy in the prevention of colon cancer and several other forms of cancer, but they also increase the risk of serious cardiovascular side effects," Dr. Levin said. "We have to strike a very careful balance between the risks and the benefits, based on a number of factors." Celecoxib is an anti-inflammatory drug that blocks the cyclooxygenase-2 enzyme, which is overproduced when cells are inflamed. An M. D. Anderson study showed a 36% reduction in the cumulative rate of colon adenoma development and a 50% reduction in larger, more dangerous adenomas with celecoxib. This study did not show an increase in cardiovascular harm, but other studies found celecoxib to double the incidence of cardiovascular harm. A parallel study led by Robert S. Bresalier, M.D., professor in the Department of Gastroenterology, Hepatology and Nutrition, using the COX-2 inhibitor rofecoxib, demonstrated a 25% reduction in new adenoma formation but a doubling of cardiovascular risk.

For now, celecoxib's potential role in chemoprevention for people at high risk of colon cancer is still being studied—alone and in combination with other agents—and the drug has yet to be recommended for widespread use. However, it has been approved by the Food and Drug Administration for use as a chemopreventive agent in people who have the condition familial adenomatous polyposis (FAP), in which hundreds of precancerous polyps form in the colon and rectum. Untreated, the inherited condition almost invariably leads to colon cancer, so the benefits of celecoxib for this high-risk population easily outweigh the risks. A clinical trial at M. D. Anderson is evaluating the safety and efficacy of using celecoxib to delay or prevent the need for a colectomy in children with FAP. Another trial at the institution is testing whether celecoxib can repair precancerous lung damage in current and former smokers.

Careful patient selection to minimize side effects is key in breast cancer chemoprevention as well, said Therese Bevers, M.D., associate professor and medical director of M. D. Anderson's Cancer Prevention Center. A large multicenter study last year showed the osteoporosis drug raloxifene to be as effective as tamoxifen in preventing estrogen-receptor–positive, invasive breast cancer—both agents reduced the incidence of breast cancer by 50% in high-risk women—but raloxifene had fewer side effects. Both drugs are selective estrogen receptor modulators, which block the effects of estrogen, an important contributor to 80% of breast cancers.

"Assessing a woman's risk of developing breast cancer and understanding how tamoxifen and raloxifene's side effect profiles compare is key in determining which to prescribe for a given woman—there isn't one right answer for everyone," explained Dr. Bevers. With tamoxifen, there is an increased risk of serious side effects such as uterine cancer, blood clots, and stroke—however, tamoxifen also decreases the risk of non-invasive breast cancer, which raloxifene does not do. A woman's menopausal status, her bone health, and other issues are also factors that should be weighed in the decision of whether to prescribe tamoxifen or raloxifene.

On the horizon

Now under investigation for their potential as breast cancer chemopreventive agents are anastrozole and exemestane. These are aromatase inhibitors, another class of estrogen blockers, which are approved to treat metastatic breast cancer in post-menopausal women.

"There is now some very solid evidence that aromatase inhibitors may inhibit or prevent breast cancer more effectively than tamoxifen or raloxifene, and a number of studies looking at this are ongoing," said Dr. Bevers.

M. D. Anderson researchers have also been involved in studies of other promising chemoprevention agents, including:

■ Erlotinib, which inhibits tumor growth by targeting the human epidermal growth factor receptor. A major study of erlotinib to prevent oral cancer in people at a high risk of developing this disease is under way at M. D. Anderson and other U.S. cancer centers. A molecular marker, loss of heterozygosity at certain critical chromosomal regions, signals increased risk. (Please see related story at right.)

■ Low-dose baby aspirin, which was shown to be modestly effective as a colon cancer chemopreventive. Dr. Bresalier was a leader of this national trial, in which baby aspirin reduced the number of new precancerous colon polyps by 19% in individuals with a history of these lesions. Baby aspirin has been shown to have cardiovascular benefits as well, although it has also been associated with an increased risk of upper gastrointestinal bleeding and stroke.

■ Curcumin (found in the curry spice turmeric), which has shown dramatic anticancer results in preclinical studies owing to its significant anti-inflammatory properties. Curcumin has been used for thousands of years in the diets of people in the Middle and Far East and therefore is believed to have a low probability of serious side effects.

■ Calcium compounds, which may inhibit tumorigenesis in the colon through their effect on dietary lipids, according to laboratory studies. A study in humans showed a 19% reduction in adenoma formation in individuals taking calcium supplements. M. D. Anderson researchers are looking at the possibility of combining calcium with vitamin D in new clinical trials.

As encouraging as some of the research has been, M. D. Anderson's chemoprevention experts stress that most current chemoprevention studies test promising agents in people who are at higher risk of developing cancer, such as former smokers, as a first step in predicting whether these agents will help those who are at average risk.

It will take decades, they say, to prove that any agent can substantially reduce the risk of a disease in the average person without unacceptable side effects. These studies will require giving healthy volunteers a drug for many years and then waiting to see whether they develop fewer cancers than those who don't use the agent. ●

Clinic Targets Oral Cancer at Early Stages

The Oral Cancer Prevention Clinic at M. D. Anderson has been established to provide early screening for premalignant lesions and oral cancers as part of the institution's cancer prevention efforts.

The focus of the Oral Cancer Prevention Clinic is on patients who have a high risk of oral cancer: those who have precancerous conditions, such as erythroplakia, leukoplakia, or oral lichen planus; those who have previously had oral cancers; and those who use tobacco and alcohol, according to Ann Gillenwater, M.D., associate professor in the Department of Head and Neck Surgery.

Beyond offering referrals for the standard treatments of premalignant lesions (observation, surgical resection, and laser ablation), the clinic enables specialists to do longer-term observation and follow-up and to collaborate on disease management. Patients also have the opportunity to enroll in clinical research trials at M. D. Anderson—both diagnostic and chemoprevention trials.

"What we're trying to do is put patients in one place where they can see the medical oncologist for cancer prevention, see a dentist for other oral pathology, have biopsies done, and if necessary, undergo treatment in one spot," said Dr. Gillenwater. "We want to eventually be able to do treatment at the clinic, if the patient is not enrolled in one of the trials."

The clinic's co-directors are Dr. Gillenwater and Vassiliki Papadimitrakopoulou, M.D., associate professor in the Department of Thoracic/Head and Neck Medical Oncology. Jack Martin, D.D.S., professor of dental oncology in the Department of Head and Neck Surgery, contributes the important perspective of a dentist.

"This is the first time that a multidisciplinary approach to oral cancer prevention is taking place in the same space," said Dr. Papadimitrakopoulou. "Dr. Gillenwater, Dr. Martin, and I are seeing patients at the same time and offering screening, biopsies, intervention, and participation in clinical trials to all appropriate patients."

Clinical trials offer patients access to cancer prevention and treatments that are not available commercially. One such study, a phase II chemoprevention trial, is testing the efficacy of rosiglitazone in the prevention of oral cancer for patients with erythroplakia and leukoplakia. Another major research effort of the clinic is the Erlotinib Prevention of Oral Cancer (EPOC) study, a National Cancer Institute–funded study whose purpose is to determine whether erlotinib prevents oral cancer in those at high risk of developing the disease. The principal investigators are Dr. Papadimitrakopoulou and Scott Lippman, M.D., professor in and chair of the Department of Thoracic/Head and Neck Medical Oncology. "This trial is unique as it is the first trial to select patients based on a molecularly defined high risk of developing cancer," said Dr. Papadimitrakopoulou.

The clinic also is evaluating new technologies to improve detection and diagnosis of oral dysplasia and early cancer, developed in collaboration with Rebecca Richards-Kortum, Ph.D., professor in and chair of the Department of Bioengineering at Rice University. Patients can enroll in several National Cancer Institute–funded trials investigating fluorescence imaging, spectroscopy, and other new methods to help clinicians identify changes associated with early cancer development.

Future plans call for an expansion of the clinic's space and the involvement of the Department of Epidemiology and the Tobacco Treatment Program.

To make an appointment, call the Head and Neck Business Center at 713-745-5146. For more information, call Dr. Gillenwater at 713-792-8841 or Dr. Papadimitrakopoulou at 713-792-6363. ●

For more information, contact M. D. Anderson's Cancer Prevention Center at 713-745-8040 or 1-800-438-6434, or visit www.mdanderson.org/topics/chemoprev/.

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Childhood cancer, though rare, is the leading cause of disease-related death among children 1 to 14 years old. Leukemias and lymphomas are the most common childhood cancers, followed by brain tumors, neuroblastomas, and sarcomas. Each year, more than 1,200 children receive treatment for these and other malignancies at the Children's Cancer Hospital, an M. D. Anderson component where clinical care and research are centered on the unique needs of pediatric patients.

"We are different from other children's hospitals because our efforts focus exclusively on cancer, and we are different from other cancer hospitals because our patients are exclusively children," said Eugenie Kleinerman, M.D., professor and head of the Children's Cancer Hospital and the Division of Pediatrics.

The whimsical décor of the Children's Cancer Hospital is paired with advanced treatments and an active program of scientific discovery. The staff assesses and treats patients at all stages of disease, from infants to those who have survived cancer from childhood into their 20s. As a result of this broad experience, Children's Cancer Hospital physicians and scientists have developed several anticancer and supportive-care treatments for children and adolescents---contributing to the national 70% cancer cure rate in these populations—and clinical trials of promising treatment regimens are ongoing.

Novel therapies

As an example of the institution's childhood cancer research, Dr. Kleinerman, Peter Anderson, M.D., Ph.D., professor of pediatrics, and Cynthia Herzog, M.D., associate professor of pediatrics, have launched investigations of the aerosol administration of chemotherapy for pediatric patients. In this approach, patients breathe in anticancer drugs using a hand-held nebulizer much like the ones used in asthma treatment. An ongoing study by Drs. Kleinerman and Anderson involves the use of aerosol-delivered cytokine therapy to treat tumors that have spread to the lungs, such as metastatic Wilms tumor.

Dr. Herzog's study involves the use of aerosol-delivered L9NC with temozolomide for the treatment of relapsed and high-risk Ewing's sarcoma.

"The goal of aerosol technology is to provide a kid-friendly treatment modality that eliminates the discomfort and inconvenience of intravenous administration and that provides children with a procedure they can learn to do on their own at home," Dr. Anderson said. Patients are trained to use the nebulizer and a lung-function monitor that records the patient's pulmonary parameters and transmits the results back to M. D. Anderson for a physician to review. Patients perform the procedure under the supervision of a nurse for an initial period. "This approach appears to be working. Our patients are pleased that they do not have to return to the hospital as often and that they can get back to school faster," said Dr. Anderson.

As part of the Children's Cancer Hospital's expanding research platform,

[redacted], 10, *takes chemotherapy through an aerosol delivery system while relaxing with a book at the Children's Cancer Hospital.*

ncer Care for Kids

neet the needs of pediatric patients. By Vickie J. Williams

Dr. Kleinerman, Dr. Anderson, *and* **Ms. Hunte** *deliver novel care in a setting that is designed to meet children's unique needs.*

new research endeavors will focus on understanding the genetic alterations in tumors, why tumor cells are resistant to chemotherapy, and the mechanisms that cause learning disabilities in children with brain tumors and neurofibromatosis.

From laboratory to clinic

Many one-time experimental therapies in pediatric oncology developed at M. D. Anderson have since moved into clinical practice. M. D. Anderson researchers designed a limb-salvage perfusion technique that is now used in more than 75% of young patients treated for malignant bone tumors. Other research resulted in the first successful chemotherapy for Wilms tumor; the nation's first neuroblastoma screening program for infants; and the first clinical trials in the United States of oral antibiotics for treatment of low-risk fever and neutropenia in pediatric patients with cancer, which opened the door for outpatient therapy. The Children's Cancer Hospital was also among the first centers to use umbilical cord blood for stem cell transplantation.

Among the many anticancer agents developed at the Children's Cancer Hospital are clofarabine, the first drug approved by the U.S. Food and Drug Administration specifically for the treatment of pediatric leukemia, and liposomal muramyl tripeptide, an immunotherapy that, when combined with chemotherapy, increases cure rates for children with osteosarcoma.

Shared resources

A major benefit of the "hospital within a hospital" structure that M. D. Anderson has adopted for pediatric care is that it fosters adaptation of adult care advances for use in children. "There are only a few large cooperative-group trials in pediatric cancer," Dr. Kleinerman said. "But M. D. Anderson conducts more clinical trials than any other cancer center in the country. We constantly monitor the results of these trials so we can incorporate therapies into our pediatric care plans as soon as they are proven safe and effective. Our patients are often the first children to have access to these novel treatments and to state-of-the-art diagnostic and therapeutic resources." Those resources include the new Proton Therapy Center, the BrainSUITE system, and positron emission tomography–computed tomography (PET-CT) fusion imaging technology.

Radiation therapy is used in the treatment of many pediatric cancers, including tumors of the brain and bone and soft-tissue sarcomas. Conventional radiation delivery can damage normal tissues, which can cause long-term side effects in children, including a decrease in bone development and in the growth of soft tissues. In many cases, children who require radiation therapy will now be treated with proton therapy. "With proton therapy, there is a higher likelihood that the radiation can be confined to the primary site, which in many cases translates into improved treatment outcomes and improved quality of life as the child grows into adulthood," Dr. Kleinerman said.

Brain tumors, which are the most common solid tumors in children, are usually treated surgically. Children with brain tumors benefit from BrainSUITE, a collection of image-guided surgery technologies that enable precise excision of complicated tumors in sensitive areas of the brain. The system provides real-time views of the tumor site during neurosurgery with intraoperative magnetic resonance imaging.

PET-CT fusion imaging improves on the capability of standard CT to detect hard-to-find tumors and is useful in monitoring therapy and communicating treatment decisions to patients and family members. "The high quality of the images produced by PET-CT fusion not only makes it easy to locate an evasive tumor but also provides information on how aggressive the tumor is, which helps us determine the best local-control strategy," said Dr. Anderson. This technology is particularly useful in the management of solid tumors.

Treating the whole child

But the Children's Cancer Hospital delivers more than just medical care. "At the foundation of our care plans is our mission to treat the whole child," Dr. Kleinerman said. "We have created physical spaces and supportive-care programs designed to provide our young patients and their family members with

(Continued on page 6*)*

Customized Cancer Care for Kids

(*Continued from* page 5)

as much normalcy as possible." In addition to a 26-bed inpatient unit and an outpatient unit, there are primary- and secondary-school classrooms, a library, playrooms, a teen lounge, an indoor recreational area with a basketball goal, a laundry room, and a kitchen.

In addition to their medical needs, pediatric patients also deal with many psychological, emotional, and developmental concerns. "We offer a host of programs designed to help our young patients understand what is happening to them, to adjust to present and inevitable changes, and to prepare for their future," said Renee Hunte, director of Child Life Services for the Children's Cancer Hospital. Many of the concerns of pediatric patients mimic those of adult patients, but children also have unique needs. "Across the board, the children's primary concerns are quality of life and getting back to school, and adolescents experience additional concerns such as body image and relationship concerns," Hunte said. "Our patients are smart. Even the younger ones will ask pointed questions—Will the treatment hurt? How long will I be in the hospital? How will radiation therapy affect me later in life? Will I die?" The Behavioral Pediatrics team, which consists of social workers, a chaplain, a psychologist, child-life specialists, and teachers, is assigned to each patient. Their goal is to cultivate an environment in which patients can express themselves freely and where questions about treatments, spiritual concerns, and life after cancer can be addressed in confidence and at an appropriate developmental level.

Certified teachers in the hospital's in-house school program work with a child's community-based teachers to make sure his or her regular curriculum is followed as closely as possible and that the transition back to the regular school environment after treatment is accomplished smoothly.

"Kids rule, not cancer"

The emphasis on social support services—and the understanding that medical care is only part of what a pediatric patient needs—ties in with the Children's Cancer Hospital mantra: Kids rule, not cancer. "We know a lot about cancer, but we also know a lot about children," Dr. Kleinerman said. "And our biggest lesson has been that kids with cancer are still just kids." ●

For more information, call the Children's Cancer Hospital at 1-888-543-2435 or 713-792-5410, or visit www.mdanderson.org/children/.

Hotline Consultation Available for Suspected Cancer Cases

Differentiating between the numerous types of cancers, recognizing the various signs and symptoms of the disease, and choosing from the assortment of diagnostic tests and treatment options available can be daunting. The challenge is especially problematic for community physicians who do not encounter the disease routinely and in the case of children. The Children's Cancer Hospital's Suspicion of Cancer Program takes some of the challenge out of these tasks by providing community physicians with a telephone consultation and referral service.

The Suspicion of Cancer Program is an information hotline that physicians can call during and after regular business hours and on weekends to speak directly with a pediatric oncologist about a case.

"The questions vary from very general to very specific," said Bill Walker, associate administrative director of the Children's Cancer Hospital at M. D. Anderson. "For example, a physician might want to discuss a patient's symptoms, get assistance in deciding which diagnostic test is appropriate, or inquire about findings on previous tests. Whatever the concern, the physician does not have to wait until the next day or for the call to be returned—he or she will have an answer right away."

The program's goal is to support the early detection and treatment of cancer. "Timing is crucial during the initial assessment period," Mr. Walker said. "The early exchange of important details between the patient's local health care provider and an M. D. Anderson specialist can facilitate timely and accurate diagnosis and treatment."

Depending on the case and the physician's particular dilemma, an M. D. Anderson oncologist might recommend that:

- The physician forward existing diagnostic test results to M. D. Anderson for review.
- Additional diagnostic tests be done locally.
- The patient come to M. D. Anderson for additional testing.
- The patient come to M. D. Anderson for consultation and treatment planning.

A referral can be requested by the physician, patient, or patient's parent and can typically be scheduled immediately. "We know that with children, it is important that any transition in care—for example, from a local setting to a cancer-center setting—be accomplished in a smooth and speedy fashion," Mr. Walker said. "Most referral appointments can be scheduled within a day or two."

Eugenie Kleinerman, M.D., professor of pediatrics and head of the Children's Cancer Hospital and the Division of Pediatrics, said the Suspicion of Cancer Program is in place to give community physicians more options in providing their patients with the best care. "We consider this program a partnership through which we not only contribute to patients' early diagnosis and make relevant treatment recommendations but also share our knowledge about cancer with community-based physicians," said Dr. Kleinerman. ●

For information about the Suspicion of Cancer Program or to contact a pediatric oncologist, call the KIDCHEK hotline at 1-888-543-2435.

HOUSE•CALL

Cancer Stages: Understanding the Basics

Going through the process of cancer diagnosis can be a dizzying ordeal, with a lot of information to process during an emotional time. Afterward, patients who have learned they have "stage III breast cancer" or "stage I melanoma" may still be unsure about what that means. Or family and friends may want to get a better understanding of what it means when a loved one has been diagnosed with "stage IV colon cancer."

An important summary

Cancer staging is an important part of diagnosis and is done to determine, as closely as possible, how far the cancer has spread when it is diagnosed. In addition to a patient's physical exam and tumor biopsy results, the doctor may get information from imaging tests such as computed tomography scans, X-rays, or bone scans, as well as from blood work and sometimes surgery. Staging is done for most types of cancer, except for leukemias and related diseases (which use different prognostic systems).

The information obtained through the staging process helps doctors determine the patient's treatment plan and prognosis. The stage is an easy-to-understand summary of what doctors have learned through the staging process, such as the size of the cancer and whether it has spread to other sites in the body.

The five stages

Most cancers can be categorized into one of five basic stages. The higher the number, the more advanced the cancer is. Each type of cancer has individual guidelines, but in general, the information in the shaded boxes applies.

Stage 0

A very early cancer that is only in the layer of cells where it started; also called carcinoma in situ.

Stage I

A small tumor that hasn't spread beyond the tissues where it arose; the cancer is localized.

Stage II

A larger tumor that may have pushed on or entered nearby structures.

Stage III

A more advanced cancer that has spread (metastasized) to nearby lymph nodes; also called a regional cancer.

Stage IV

A cancer that has spread to organs distant from the original site; also called distant metastasis.

Patients should remember that staging is a planning tool to guide treatment, not a definite indication of outcome.

Some types of cancer, such as those of the breast and pancreas, are further categorized within the stages---for instance, stage IIa or stage IIIb. For more detailed staging information specific to each cancer type, go to www.cancer.gov/cancerinfo/pdq and click on "PDQ: Cancer Information Summaries: Adult Treatment." From there, select a type of cancer and then click on the "Stages" link.

It's also helpful to know that when a cancer has spread to another part of the body, the type of cancer doesn't change. For example, a breast cancer that has spread to the bones is considered a metastasized breast cancer, not a bone cancer.

One of many factors

Patients should remember that staging is a planning tool to guide treatment, not a definite indication of outcome. Many other factors go into each patient's outcome, including age, overall health aside from cancer, quality of medical care, adherence to the treatment regimen, genetics, and other factors. ●

For more information, talk to your physician, or:

- *call* askMDAnderson *at 1-877-632-6789*
- *visit www.mdanderson.org.*

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DiaLog | Rethinking the Standard of Care

By Michael Fisch, M.D., M.P.H.

The "standard of care," as defined by the dictionary, is "a diagnostic and treatment process that a clinician should follow for a certain type of patient, illness, or clinical circumstance." It is easiest to identify for any medical process that is both readily available and appears to be entirely satisfactory as it currently stands, and when there is widespread agreement that innovation is not needed. For example, it is the standard of care to insert a catheter into a vein for any patient who requires intravenous fluids or the administration of intravenous medications.

In contrast, the standards of care for cancer patients are often difficult to discern, challenging to apply, and surprisingly variable based on the location of care—and they can have devastating limitations for some patients.

Consider the standard of care for advanced pancreatic cancer, a deadly disease with a median overall survival in the range of 2 to 6 months. This grim fact is not substantially different than it was 15 years ago, despite the development of newer chemotherapy options. The standard of care is thus disappointing for most patients with pancreatic cancer. For other patients, the standard of care may not even be an option because it is too costly or not available in certain regions or health systems.

The standard of care could be seen more as a space than as a point. It reflects care that is in general accord with the patient and family's wishes and is also reasonably consistent with local clinical, cultural, and ethical standards. The standard of care is to be identified and acknowledged. But when it is associated with outcomes that are too limited, we need to offer our patients the opportunity to escape from it.

The key to this escape is to strive to get beyond the potentially devastating limitations of the standard of care, making certain that there is innovative, carefully monitored, expertly conducted clinical research that provides patients in all settings with a superb clinical trial to contrast with the standard of care. Patients also deserve clinical trial options for nausea, pain, distress, and other difficult problems.

Trials are, of course, filled with uncertainty. But so long as care occurs in an envelope of compassionate clinicians working in an effective team along with a plan for continuous quality improvement, there is reason to be hopeful. ●

Dr. Fisch is director of M. D. Anderson's General Oncology Program, an associate professor in the Department of Gastrointestinal Medical Oncology, and chair of the OncoLog Editorial Board.

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