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REPORT TO PHYSICIANS

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PHASE I CLINICAL TRIALS PROGRAM

Moving New Drugs from "Bench to Bedside and Back"

by Sunni Hosemann

GOOD NEWS: *There is a veritable explosion in the development of new investigative cancer treatments.*

BAD NEWS: *The lengthy testing and approval process means it can be a number of years before promising new treatments make it into clinical practice.*

"New drug development has exploded in recent years," said Luis H. Camacho, M.D., assistant professor in the Phase I Clinical Trials Program at The University of Texas M. D. Anderson Cancer Center. "If you look at applications for Food and Drug Administration (FDA) approval of oncology drugs, you see an increase not only in the number of individual agents, but also in the different classes of drugs for cancer treatment," he added. In addition, he points out that submissions for presentation at the American Society for Clinical Oncology (ASCO) meetings involving phase I studies of new drugs and new drug combinations increased by 61% during a recent 3-year period. Dr. Camacho sees this as encouraging news for physicians, for patients, and for patient advocates.

For him, the question then becomes: "What can we do to make sure that the fruits of these studies get to patients sooner?"

Although everyone—pharmaceutical sponsors, physicians, and most of all, patients—wins when a new cancer treatment becomes available, no reasonable person wants a treatment that is not thoroughly tested for safety and efficacy. These safeguards mean the journey from laboratory discovery to clinical use can be lengthy. Protocols must be developed, patients enrolled and treated over time, data collected, analyzed, published, and reviewed,

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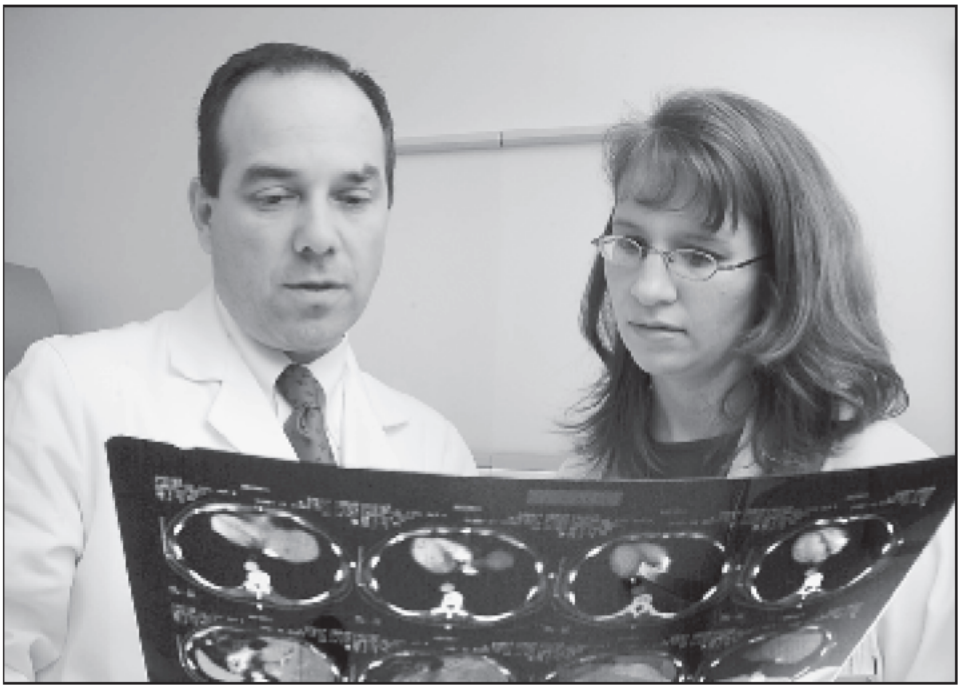

Dr. Camacho *and* **Marilise Berniger,** *physician assistant, assess tumor responses.*

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and studies replicated in larger groups. This takes time. Too much time, some doctors say, in situations where there are currently no good options for seriously ill patients.

So, how do we hasten this process without sacrificing science? About 2 years ago, M. D. Anderson physicians Waun Ki Hong, M.D., professor and head of the Division of Cancer Medicine, and Razelle Kurzrock, M.D., professor of medicine and director of the Phase I Clinical Trials Program, identified phase I trials as one of the bottlenecks in the chain of events "from bench to bedside" and saw an opportunity to shave some important time off of the process. Thus was conceived the Phase I Clinical Trials Program, in which phase I trials of promising new therapies enroll patients with different tumor types. One of the goals of the program is to look for response during the phase I trial and then fast track drugs that induce responses in patients with a specific type of advanced cancer into a larger phase II efficacy trial. Dr. Kurzrock points out that this cross-disease approach may hasten potentially beneficial drugs through the process by increasing the number of high-impact protocols. The Phase I Clinical Trials Program provides:

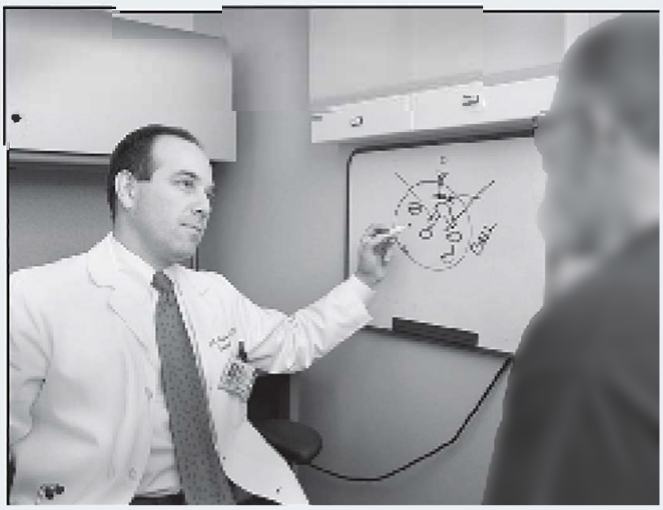
- A portal of entry for referring physicians, for patients who may not be sure where to look for a trial, and for patients for whom all standard therapy has failed.
- Both inpatient and outpatient facilities dedicated to administering phase I studies in which patients can receive first-in-human investigational drugs, novel dosing schedules, or new combinations of FDA-approved or experimental drugs.
- A home for trials of agents that cross disease boundaries—studies that, according to Dr. Kurzrock, "could be done anywhere or everywhere and thus end up being done nowhere." She added, "The program provides the infrastructure for the concerted effort it takes to get these studies done, and in some cases facilitates a faster than normal move to phase II and III studies." This happened recently for a novel antiangiogenic

Examining Concerns About Phase I Trials

Phase I studies have been perhaps the most controversial of clinical trials, laden with myth and misconception, as well as true ethical concerns, and are thus perhaps the most difficult to explain to patients. Some of the questions are as follows:

Q Phase I trials are first-in-human studies. Do they therefore represent unacceptable unknowns?

A Today, phase I studies are not all tests of unknown agents. Many investigate approved drugs in novel combinations or dosing schedules; many agents under investigation are for the sole purpose of finding drugs with fewer side effects. So, these trials can't all be painted with the same brush. The expectations vary according to the study, and each must be assessed individually. In addition, because many of the newer drugs are being studied for the first time in humans, the drugs have been developed in a very rational way and have fewer side effects than standard therapies. "Most importantly, patients with terminal disease often request access to experimental agents, even when they know the drug has not been studied before in humans," said Dr. Kurzrock. "For them, the risks associated with the drug are eclipsed by the known course of their illness."



Dr. Camacho *discusses the mechanism of action of new treatments with his patient,* [redacted].

Q The purpose of phase I trials is to find the appropriate safe dose of a drug. Does this mean that escalating doses are given until toxicity is reached?

A According to Dr. D. Hong, "Today, we are looking not only for the maximum dose a patient can tolerate, but for the *optimal biologic dose*—the dose that brings about a tumor response." In fact, he says that some scientists now argue that determination of maximum tolerated dose is no longer needed. Today, tumor response plays a central role in phase I studies, largely due to advances in technologies—imaging techniques like combination positron emission tomography, computed tomography, and dynamic contrast magnetic resonance imaging scans and molecular analysis of proteomic and genomic profiles, for example—that enable investigators to evaluate not only the patient's but the cancer's response to a drug. This is a major shift in emphasis for phase I trials, and the result is that investigators are emerging from phase I trials with far more sophisticated information than ever before. Finally, for those trials in which escalation occurs until toxicity is

compound in which investigators noted tumor responses in sarcoma, thyroid, and renal cancers, plus a low incidence of side effects. The agent has already been streamlined into phase II trials for both sarcoma and thyroid cancers. Since mouse models did not identify these tumor types as promising targets for clinical trials of the agent, these diseases would not have been the focus of single-disease trials. The cross-disease approach allowed the investigators to more quickly identify where the agent might have promise in humans and move forward from there.

- A stimulus for research into promising agents for some of the less common cancers. It is more difficult to accrue sufficient numbers of patients who have some of the rarer cancers—neuroendocrine cancers, for example—which puts research even further behind for these cancers. "Nothing drives significant research like seeing a response," said Dr. Kurzrock.

- A mechanism for sharing and disseminating timely information to colleagues. Dr. Camacho and colleagues authored a study earlier this year that found that the publication of phase I study results took a median of over 3 years, with a significant percentage published more than 5 years after completion of the study. (Lack of time and author relocation were among the

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"In some cases, the program facilitates a faster than normal move to phase II and III studies."

– Dr. Razelle Kurzrock

reached, patients are closely monitored for safety. Recent surveys of patients also indicate that many prefer higher doses, even at the risk of toxicity, if the chance of response is also higher.

Q The participants in phase I trials are often cancer patients whose disease has proven refractory to standard treatments and who have exhausted other possibilities for treatment. Are these patients potentially vulnerable to exploitation?

A "When I see a patient who is interested in a phase I trial, I want to know what their understanding of their disease is and what their goals are," said Dr. Hong. "It's very important to determine whether those goals are consistent with what they can realistically hope for from a particular study.

"This is not a time for false promises," he added. That said, however, he pointed out that there are many new and promising agents in the pipeline—immune modulators, new chemotherapies for renal and liver impaired patients, antiangiogenic agents, drugs that can target metastatic brain lesions, and unique combinations of different types of agents.

And the new agents *are* benefiting patients. Until recently, it was thought that there was very little hope of personal benefit for participants in a phase I trial; the response rate was thought to be about 4%. Many assumed that the people who participated in these trials did so with little hope for personal gain, but rather to make an altruistic contribution to medical knowledge by volunteering to be a "guinea pig."

But in fact, a recent review of all phase I studies conducted under the auspices of the National Cancer Institute showed a response rate of 10.7% and a partial response or stabilization of disease in an additional 34.1% of patient participants, meaning that 44.7% of patients benefited from these trials.

The question is not whether phase I trials are ethical or beneficial but whether a particular one makes sense for an individual patient. In many cases, they do. Consider one patient with metastatic renal cancer who is participating in a trial of a new oral form of platinum that has no liver or kidney toxicity. Because he lost one kidney in an accident and the other to renal cancer, he is not eligible for many trials or for some standard chemotherapies that could help him. He was quite pleased to find a trial that could include him.

Another patient in his eighties had progression of disease despite standard treatments for medullary thyroid cancer, and is now in a phase I trial of an antiangiogenic agent. His tumor is shrinking, and he reports that his current quality of life is "outstanding."

Consider a 39-year-old breast cancer patient with liver metastasis who had a life expectancy of about 3 months when she entered a phase I trial 3 years ago. Thanks to a hepatic regional treatment (intra-arterial hepatic infusion) for liver metastases, the woman is alive and well today and has devoted herself to helping other women fight breast cancer. (She developed the [redacted] Foundation in [redacted].)

No one would make the case that phase I trials are for everyone. Certainly they're not for a patient who has a stage and type of cancer for which there are good standard treatments. However, the truth is that many patients with metastatic cancer have exhausted their options or have only standard options that have poor efficacy and high toxicity. "Most importantly, patients tell us time and again that their quality of life is improved just by trying something," said Dr. Kurzrock. "They understand that the chances are slim, but they don't want to give up, and they don't want their physician to give up on them either." ●

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most common obstacles for the delayed publication of these studies in peer-reviewed literature.) Such delays mean a loss of momentum and possible missed opportunities to build on promising studies. And, because drug patents for investigational agents expire, untoward delays could conceivably prevent a drug from coming to market at all.

- A platform for moving toward the new frontier in cancer research, personalized therapy. As an example, David Hong, M.D., assistant professor in the Phase I Clinical Trials Program, is conducting a study that combines two experimental agents that target different signaling pathways. This is a particularly relevant study, since many tumors may rely on more than one pathway to survive, and one drug alone may not be enough to kill the tumor. As part of this study, Dr. Hong will be performing extensive molecular profiling of tumor tissue to determine if specific characteristics correlate with response. Preliminary data of this type gathered in phase I can set the stage for phase II efficacy studies that determine not just response rates but also which patients are most likely to respond.

The definition of a good idea might be that in hindsight it seems obvious. If so, the Phase I Clinical Trials Program surely is one. So far, the program has seen an increase in the number of protocols and in inquiries from patients and physicians, has seen successes in trials, has streamlined the transition from phase I to phase II trials, and perhaps most importantly, has provided new options for people with advanced cancer. ●

For more information, *contact Dr. Kurzrock at (713) 794-1226, Dr. Camacho at (713) 745-5252, or Dr. D. Hong at (713) 563-5844. More information about the Phase I Clinical Trials Program is available at www.mdanderson.org/departments/phase1/.*

IN BRIEF

Elderly Patients May Benefit from Chemotherapy

Patients 80 years and older with non-small cell lung cancer (NSCLC) can tolerate and may benefit from standard chemotherapy, say researchers at M. D. Anderson Cancer Center.

The life expectancy of an 80-year-old man is 87.3 years and of a woman is 89.0 years. Therefore, when 80-year-old patients with advanced NSCLC are not treated, they are robbed of years of life.

However, there are almost no data about the effectiveness of chemotherapy in lung cancer patients 80 years and older, even though they constitute 17.8% of all lung cancer patients in the U.S. In addition, more than 50% of cases of advanced NSCLC are in patients older than 70 years, and while there are some data on treating patients up to 70 years old, little has been known to date about the impact of chemotherapy on NSCLC patients 80 years and older. In the first known study of its kind, Ralph Zinner, M.D., assistant professor in the Department of Thoracic/Head and Neck Medical Oncology, and Ozden Altundag, M.D., conducted a retrospective review of 46 chemotherapy-naive advanced NSCLC patients treated at M. D. Anderson between 1997 and 2004 to determine the effect of chemotherapy on people 80 years and older.

Researchers compared older patients (80 years and older) with those below 80 years and found similar response rates between the two groups, which suggests that many of the older patients did benefit from the chemotherapy. However, it was also observed that patients over 80 years old were less likely than younger patients to seek treatment at M. D. Anderson, indicating that the older patients may have been in better condition than the typical patient in this age group. Nonetheless, according to Dr. Zinner, "these results, though preliminary and retrospective, are encouraging and support the hypothesis that physiological age rather than calendar age should be the key determinant of whether to treat patients, even those 80 years and older." Specifically, the study found the following among its patients:

- A clinical response was observed in 41% of patients in the older group and 47% of patients in the younger group.
- The rate of second-line chemotherapy was similar for both the older and younger patients (41% vs. 45%).
- Toxicity was not significantly different between the older and younger patients.
- Dose reduction was not significantly different between the older and younger groups (22% vs. 14%).
- Chemotherapy was delayed due to toxicity at least once in 20% of both older and younger patients.

Patients 80 years and older with NSCLC are often excluded from clinical trials because there is concern about the safety and effectiveness of treating them with chemotherapy. However, the data from this study encourage researchers to investigate whether patients 80 years and older who are in good condition would benefit from standard chemotherapy as well as novel agents in clinical trials.

COMING UP

Oncologic Emergencies Conference, 2006
January 20-21, 2006

M.D. Anderson Cancer Center
Houston, Texas
Program Chair: Ellen Manzullo, M.D.

This conference is targeted to physicians in internal medicine, emergency medicine, and oncology. For more information, visit www.mdanderson.org/prof_education/cmecs or call CME/Conference Services at (713) 792-2223, toll free at (866) 849-5866.

HOUSE•CALL

When the End Is Near

Ways to Cope When a Loved One Is Terminally Ill

The news that a loved one's cancer has advanced and that his or her life is nearing an end can be devastating for friends and family members. The immediate concern will be for the patient's well-being; caregivers often overlook the emotional and physical strains the prognosis imposes on them. Described here are tips to help people cope with the impending death of a loved one.

Talk—and listen.

Laugh over the good times you have shared. Reminisce about special occasions. Resolve any old conflicts. "Talking about happier times and making amends for disputes and disappointments can be therapeutic for both parties," said Donna Zhukovsky, M.D., associate professor in M. D. Anderson Cancer Center's Department of Palliative Care and Rehabilitation Medicine. "Discussion of the good times will linger once the person is gone, and the resolution can be healing."

Support the patient's choices.

Friends and family members must respect the patient's right to make decisions about end-of-life care, even when the parties disagree. "For some patients, holding on to hope might mean deciding to exhaust every possible anticancer treatment option," said Dr. Zhukovsky. "Others ask simply to be made comfortable for the time they have left." Decisions are best made in the context of what it means to the person. For example, some people choose aggressive treatments that carry the risk of unpleasant side effects in an effort to prolong life long enough to participate in a special life event, such as the birth of a grandchild, a bar mitzvah, or a college graduation.

Knowing what your loved one would like in certain situations relieves a lot of stress if you need to make those decisions.

Set goals for your role in supporting the patient.

Once the patient's preferences are clear, Dr. Zhukovsky encourages them and their family members to set goals. "By setting goals, each party determines what to do to make sure the specified end-of-life wishes are realized," she said. "I encourage friends and family members to pattern their goals to match the patient's goals." For example, if the patient's end-of-life preference is to be made comfortable to the end, family members can determine what to do to create a serene environment, such as placing family photographs close by and playing the patient's favorite music. Large goals can often be broken down into smaller components that are more easily achievable, allowing the patient to see the progress and feel a sense of accomplishment.

Be informed.

As difficult as it is, talk with your loved one about his or her feelings on end-of-life issues. "Toward the end, patients may not be able to communicate well," said Dr. Zhukovsky. "Friends and family members may be required to speak or make decisions on the patient's behalf. Having some familiarity with the issues likely to arise will be useful." Common decisions include those surrounding the intensity of treatment the patient would like to receive in certain situations, for example, the use of hemodialysis for people in kidney failure or the use of respirators for people who can no longer breathe on their own, as well as the preferred location of death—at home or in an institutional setting. Knowing what your loved one would like in certain situations relieves a lot of stress if you need to make those decisions.

Take care of yourself.

Caring for people who are terminally ill can be physically and psychologically daunting. Dr. Zhukovsky advises caregivers to seek professional counseling if they experience emotional distress. "Support for caregivers is now recognized as an important component of palliative care and comes in many different forms," she said. "Many hospitals offer programs to help caregivers cope." The social work staff is a valuable resource for information about hospice care or in-home nursing and for information about financial assistance. Bereavement counseling and emotional support are offered by psychotherapists; the hospital's chaplain is a resource for spiritual support.

Dr. Zhukovsky said that support for the companions and relatives of people who are terminally ill has become recognized as an important component of palliative care. "We try to deliver care forthrightly, with honesty and compassion," she said. "We acknowledge the reality, but then we move on to the positive." ●

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

(800) 392-1611, Option 3, *within the United States, or*

(713) 792-3245 *in Houston and outside the United States.*

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V. Williams

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After Katrina

Caring for cancer patients in the wake of the storm

by Dianne Witter

Hurricane Katrina's wrath was far-reaching when it slammed into the Gulf Coast regions of Louisiana and Mississippi in late August. People fled a city in chaos, some able to take only what they could grab and carry with them; others, not even that. For those already undergoing treatment for cancer, it was a second storm of life-threatening proportions.

As well over 20,000 evacuees poured into the city of Houston, patient care leaders at M. D. Anderson implemented a plan for managing the immediate oncological needs of evacuees. In the weeks following Hurricane Katrina, M. D. Anderson admitted or treated 353 cancer patients affected by the storm—44 who were admitted to the hospital, 236 who contacted or were registered in the outpatient clinics, and 62 who were treated and released from our Emergency Center.

Many evacuees who made their way to M. D. Anderson seeking treatment had only sketchy information about the medical details of their diagnosis and the treatments they'd had, and there was slim chance of contacting their doctors—many of whom were displaced themselves. For a patient scheduled for surgery to remove a fast-growing malignancy, or one who has been diagnosed with a new metastasis, medical care is critical, and a good medical history even more so.

"Our patient care teams had to get creative to piece together the details of patient's medical treatments—what chemotherapy or clinical trial they were on, or the details of surgery and radiation," said Thomas Burke, M.D., executive vice president and physician-in-chief for M. D. Anderson. "Patient admissions specialists tracked down key information based on each patient's verbal medical history, physician's names, and insurance companies."

From there, the specialists posted messages on the American Society of Clinical Oncology Internet message board asking patients' doctors to contact them. Insurance companies sometimes were able to help with information about a patients' medications and dosages, or to trace information about tests back through the laboratories that had billed the insurance companies. For evacuees without their insurance cards and little cash, M. D. Anderson's pharmacy often waived copays and paperwork. Often, getting evacuees the cancer care they needed meant staying flexible and finding new solutions.

For M. D. Anderson—and other medical centers treating evacuees throughout the country—it was a true test of agility during a crisis. ●

OncoLog, M. D. Anderson Cancer Center's report to physicians, is a monthly newsletter sent to more than 30,000 physicians throughout the nation and the world. Published by the Department of Scientific Publications, *OncoLog* reports on innovative developments in research and treatment at M. D. Anderson. Current and previous issues are available online in English and Spanish at www2.mdanderson.org/depts/oncolog. For editorial information, call (713) 792-3305 or email scientificpublications@mdanderson.org. To refer a patient or request information, call (800) 392-1611 or (713) 792-6161, or visit www.mdanderson.org.

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