Researchers Examine Link Between Stress and Response to Cancer Treatment

by Beth Notzon and Janette Weaver

Diagnostic tests, a cancer diagnosis, prolonged therapy, treatment side effects, debilitating symptoms, financial concerns, family worries—the sources of stress that patients with cancer encounter seem limitless. And although the stress response itself “is first and foremost an adaptive or normal response,” said Lorenzo Cohen, Ph.D., an assistant professor in the Department of Behavioral Science at The University of Texas M. D. Anderson Cancer Center, chronic stress can have serious consequences for patients with cancer.

There is growing evidence that stress—the way in which one responds to stressful life events—can not only lower the quality of life in patients with cancer but can also profoundly affect physiological functioning and may affect how the disease responds to treatment.

The possibility that stress negatively affects treatment response is of particular concern with regard to tumor vaccines because one of the cardinal observations in the area of stress and immune function research, called psychoneuroimmunology, is that stress dysregulates the immune system. In particular, the number and function of natural killer cells decreases, TH1 cytokines are suppressed, and the level of TH2 cytokines (e.g., interleukins)

(Continued on next page)
Link Between Stress and Cancer Studied
(Continued from page 1)

4 and 10) rises significantly.

Reasoning that in patients who are highly stressed, an immunogenic tumor such as renal cell carcinoma might not respond as well to a vaccine designed to boost the immune response, Dr. Cohen and his co-workers measured subjective stress levels in 30 patients with renal cell carcinoma treated with the autologous heat shock protein peptide 96 vaccine (HSPPC-96) (described in the March 1999 issue of OncolLog).

“Our hypothesis was that patients who are more distressed are going to have suppressed cell-mediated immunity going into treatment, and therefore, the treatment might not be as effective,” said Dr. Cohen.

To determine stress levels, patients completed a 14-item scale that measured the degree to which they saw their lives as unpredictable, uncontrollable, and overloaded. Dr. Cohen’s group discovered a negative association between stress levels at the start of treatment and patients’ in vitro immune responses to their autologous tumor targets. Thus, patients with higher stress levels at the start of treatment had immune systems that were less able to fight the tumors.

“The preliminary analysis suggests that the patients who were less distressed had an increased immune response to their own tumor,” Dr. Cohen said. “The association remained significant even after we took into account the severity of the individual’s disease because we believed that the patients who had more severe disease would be more immunosuppressed and more distressed.

“Once the results of the clinical trial are published, we will be able to report on the association between perceived stress and treatment response,” Dr. Cohen said.

Although the findings are preliminary and require more extensive study, Dr. Cohen believes that they point clearly to stress as a culprit in reducing psychological and physiological functioning. There is even some evidence emerging from other laboratories suggesting that stress contributes to the progression of cancer.

Further insight into the effects of stress on physiological functioning has come from Healthy subjects. Dr. Cohen, in collaboration with Qingyi Wei, M.D., Ph.D., an associate professor in the Department of Epidemiology at M.D. Anderson, and Gailen Marshall, M.D., in the Department of Internal Medicine at The University of Texas–Houston Medical School, studied the DNA repair capacity in healthy medical students during exam time, when stress levels were high, and then immediately after a vacation break, when students were more relaxed. The DNA repair capacity gauges cell repair activities, and a heightened DNA repair capacity signifies increased DNA damage. Of far greater importance, however, it indicates the increased formation of damaged cells that in the presence of a faulty repair capacity and suppressed cell-mediated immunity could proliferate and lead to carcinogenesis. This study showed that, in fact, the DNA repair capacity in subjects was 26% higher during the exam period.

Findings such as these from the research of Dr. Cohen and others are being put to several practical uses. One is to define predictors of poor long-term psychological functioning, which could identify patients who might need some type of psychological intervention. Another focus is to develop more effective ways to lower stress and improve quality of life in patients with cancer. In one such effort by Dr. Cohen and his colleagues, palm-top computers are being tested in patients with breast cancer to supplement a traditional stress management program that encourages the use of and provides information about effective cognitive and behavioral stress management techniques.

“The preliminary analysis suggests that the patients who were less distressed had an increased immune response to their own tumor.”

– Lorenzo Cohen, Ph.D., assistant professor, Department of Behavioral Science

In another study begun two years ago, Dr. Cohen is examining the benefits of presurgical stress reduction in men with early-stage prostate cancer. Thus far, 80 men have been enrolled in the study and randomized into one of three groups. Danielle Devine, Ph.D., a research associate in the Department of Behavioral Science, explained that the first group meets one-on-one with a clinical psychologist and is taught relaxation skills such as guided imagery, deep-breathing exercises, and other coping strategies for stress management.

The second group receives the same amount of individual time with a clinical psychologist as the first group, but the treatment consists of supportive attention, rather than specific relaxation and coping skills training. The third group, the control group, receives no psychosocial intervention. Dr. Devine explained that it is too soon to draw any firm conclusions from the study, but if willingness to participate is any indication (about 80% of eligible men agreed to take part in the study), patients do recognize a need for research on stress intervention. Also, anecdotally, men in both intervention groups have indicated that meeting with someone before surgery helped manage their stress, Dr. Devine said.

Other ongoing stress-related studies aim to examine different psychological and biological mechanisms that may be associated with quality of life, treatment response, disease progression, and survival. These research efforts include a study of biobehavioral factors in patients with ovarian cancer, a study of biobehavioral factors as predictors of mortality in patients with metastatic renal cancer, an examination of stress...
And quality of life in patients participating in phase II clinical trials, and a study of an emotional expression intervention for patients with renal cell carcinoma. A pilot study of a Tibetan yoga-based intervention for patients with lymphoma is also underway.

Studies of age-old techniques such as yoga illustrate that, like everything else under the sun, there is nothing new about the perceived role of stress in disease. Dr. Cohen noted that the ancient Greeks recognized the concept of a healthy mind in a healthy body. "They knew that sleep was important, that appropriate nutrition was important, as was having an appropriate balance in one's life. They even used massage therapy and music therapy," he said. Many of these approaches are being revisited in more modern guises at the M. D. Anderson facility called Place . . . of wellness. Founded a little more than two years ago, the Place . . . of wellness is the first on-site, free-standing facility within a comprehensive cancer center to offer complementary therapies and programs for patients with cancer and their personal caregivers. It is open to anyone receiving cancer care—not just M. D. Anderson patients—and their families at no cost. In the past year alone, more than 8,100 patients and family members took advantage of 1,047 programs ranging from yoga and art therapy to nutrition and education.

"We offer anything that helps develop the openness between the person and their spirit and emotions and offers an outlet for expression of what they are going through," explained Judy Gerner, director of Anderson Network Patient Services. Gerner is working with Dr. Cohen to make these types of programs part of the treatment plans of more cancer patients. However, she makes it clear that they do not claim that the programs can cure disease. "These programs are designed to complement traditional medical care and focus on the healing ability of the mind, body, and spirit," she explained.

FOR MORE INFORMATION, contact
Dr. Cohen at (713) 745-4260.

Behavioral Science Research Activities

Studies of psychosocial assessments and interventions led by faculty in the Department of Behavioral Science include the following.

- Increasing physical activity in breast cancer survivors (BS97-341). Principal Investigator: Karen Basen-Engquist, Ph.D.
- Reproductive health needs in African-American breast cancer survivors (ID00-058). Principal Investigator: Leslie Schover, Ph.D.
- Mood and quality of life associated with follow-up monitoring and CA 125 testing for women with ovarian cancer (ID98-153). Principal Investigator: Lorenzo Cohen, Ph.D.
- A physical activity quality-of-life intervention for patients with androgen-ablated prostate cancer (BS97-048). Principal Investigator: Ellen R. Gritz, Ph.D.
- Seeking help for sexual problems after prostate cancer (ID99-237). Principal Investigator: Leslie Schover, Ph.D.
- Presurgical stress reduction, mental health, and cancer (BS97-278). Principal Investigator: Lorenzo Cohen, Ph.D.
- A Tibetan yoga-based intervention program for patients with cancer (ID00-410). Principal Investigator: Lorenzo Cohen, Ph.D.
- The effects of depression, social support, and spirituality on the survival of patients with metastatic renal cell carcinoma (ID99-381). Principal Investigator: Louis Pisters, M.D.
- The development of interactive media to provide patients with information about banking sperm before cancer therapy (ID99-365). Principal Investigator: Leslie Schover, Ph.D.
- Adjustment and health behavior in survivors of testicular cancer (BS99-017). Principal Investigator: Karen Basen-Engquist, Ph.D.
- An intervention to encourage patients to seek help for sexual problems after prostate cancer (ID00-400). Principal Investigator: Leslie Schover, Ph.D.
- Effect of prostate cancer on spousal relationships and quality of life (BS99-176). Principal Investigator: Cindy Carmack, Ph.D.
- Neurocognitive function and quality of life after testicular cancer treatment (BS98-323). Principal Investigator: Ellen R. Gritz, Ph.D.
- Patient satisfaction and psychological distress related to emerging technologies for cervical cancer screening and diagnosis (BS98-269). Principal Investigator: Karen Basen-Engquist, Ph.D.
Moving Toward Recovery: Exercise Video Features Adolescents with Cancer

by Kerry L. Wright

It begins with a warm-up, followed by 45 minutes of nonimpact aerobic resistance training with two- to five-pound weights—working seven of the body's main muscle groups for five minutes each—and finally ends with a slow cooldown.

Although it sounds like a typical workout at the neighborhood gym, the exercisers are 10 adolescent patients recovering from musculoskeletal cancers, the location is the brightly painted PediDome at The University of Texas M. D. Anderson Cancer Center, and the occasion is the taping of an exercise video designed to enhance the recovery process in patients with cancer.

"I was making rounds, visiting some of my patients who were on treatments, and all these kids were sitting in front of the computer, e-mailing or on the Internet, or sitting watching movies in the room, and I just thought, 'How depressing to sit there hour after hour, day after day,'" said Eugenie S. Kleinerman, M.D., the newly appointed head of the Division of Pediatrics and a professor in the Department of Cancer Biology at M. D. Anderson. As Dr. Kleinerman is also a certified fitness instructor, she thought, "I know how much better I feel when I get up and do something. So you know, it really would be nice if we could have some kind of exercise program [for these kids]."

With the support and financial backing of the Silver Grace Hope Foundation, a local nonprofit organization "dedicated to providing hope, joy, and peace to children of all ages," the first step in the development of an exercise program for adolescents recovering from cancer has been completed—recording the exercise video.

On the morning of February 4, 2001, the 10 adolescents, all of whom were being treated or had recently completed treatment for sarcoma, gathered at M. D. Anderson for the taping.

The patients, who ranged in age from 12 to 19, had undergone various treatments, including surgery (often involving amputation or reconstruction of a limb) and chemotherapy.

"It’s hard for them. Their bodies are worn down from the medicines," said Kristy Weber, M.D., an assistant professor in the Section of Orthopaedic Surgery in the Department of Surgical Oncology, who also attended the taping and was involved in making sure the exercises were safe. She had performed surgery on many of the teenagers and was therefore aware of any restrictions on their movements. For some participants, modifications were made so that they could perform the exercises; others had to sit out during short sections of the taping.

Dr. Kleinerman plans to use the video to establish an exercise program at M. D. Anderson that gets patients to start exercising in the hospital so that they can continue when they return home. "We thought it would be more motivating to have kids with cancer in the video," she said. In that regard, Dr. Kleinerman wants to see if having the video at home prompts teens to exercise more routinely than they would otherwise and if they would rather use the video than go to the physical therapist several times a week.

After initial field testing to see how adolescents respond to the video, Dr. Kleinerman hopes to extend the project to younger children, to parents of children in the hospital, and to patients with other types of cancer. In the long run, she also plans to conduct a study in which recovering patients are randomized into either an exercise group or a control group, after which quality of life and recovery from surgery, among other measures, will be assessed.

Although rest has traditionally been advised after cancer treatments, a study published in 1997 in the journal Cancer showed that of patients who had undergone chemotherapy, those who participated in an aerobic exercise program had better physical performance, higher levels of hemoglobin, and less fatigue than those who were not exercising regularly. Similarly, a 1998 study in the Journal of Strength and Conditioning Research showed that patients who had undergone chemotherapy and participated in a 10-week wellness program were stronger and had more endurance than patients who were not involved in the program.

"I think the only way [an exercise program] is going to become accepted and standard practice is if we can show data that it benefits the patient," said Dr. Kleinerman. "I just think it’s very important in the recovery process and probably in promoting and maintaining a positive body image for these kids."

For more information, contact Dr. Kleinerman at (713) 792-8110.
Getting the Facts About Clinical Trials

Deciding whether to participate in a clinical trial can be one of the most important choices a patient with cancer makes. Patients who take part in research studies have an opportunity not only to help themselves but also to help improve care for other patients with cancer. But because clinical trials involve experimental treatments, some patients are distrustful of them, and misconceptions are common. Knowing the facts about clinical trials can help you decide if participating in a trial is right for you.

FACT: A clinical trial is a carefully planned and approved research study. The National Cancer Institute defines a cancer clinical trial as an organized study conducted in people with cancer to answer specific questions about a new treatment or a new way of using an old treatment. Participants are divided into groups that receive different treatments to determine which is the best one. All clinical trials must be approved by an institutional review board, which reviews the study for ethical and patient protection issues. At the MD Anderson Cancer Center, a clinical research committee also reviews each clinical trial.

FACT: Clinical trials are the only way to medically evaluate proposed new treatments for cancer. Laboratory studies can indicate that a new treatment may benefit patients, but such results must be tested and verified in humans. Without clinical trials, no new drugs or therapies can be approved for use in people with cancer.

FACT: All studies must be thoroughly explained to the participants, who have the right to ask questions about any aspect of the study or their participation. A patient who wishes to take part in a clinical trial must sign an informed consent form, which outlines the purpose of the study, describes what will happen, lists possible risks and benefits (as far as these are known), and names any alternative procedures or treatments that are available without participating in the study.

FACT: Taking part in a clinical trial is always completely voluntary. No patient is ever denied standard care or in any way discriminated against for not taking part. A participant is always free to leave the trial at any time or to decline any part of the treatment.

Advantages and Disadvantages of Participating in a Clinical Trial

Advantages:
- Study participants are closely monitored.
- Participants may be among the first to receive new treatments.
- Being part of a clinical trial makes some patients feel more in control of their lives and their illness.
- Participants are actively joining the fight against cancer, both for themselves and for future patients.

Disadvantages:
- Clinical trials can have unknown dangers and side effects that sometimes occur long after the conclusion of the study.
- The additional tests and monitoring involved in clinical trials, as well as new or experimental treatments, may not be covered by insurance.
- The new treatment may not be any more effective, or may be less effective, than existing treatments.

For more information about specific clinical trials, visit the National Cancer Institute Web site at cancertrials.cancer.gov. A booklet on clinical trials, upon which much of this article was based, is available on the Web at cancertrials.cancer.gov/understanding/booklet/treatment/intro.html or from the Cancer Information Service at (800) 4-CANCER.

For information about clinical trials at the MD Anderson Cancer Center, visit http://www.clinicaltrials.org.

Important Questions

Before patients decide to participate in a clinical trial, the National Cancer Institute advises getting satisfactory answers to the following questions:

+ What is the purpose of the study? Who sponsors it? Who has approved it?
+ What specific tests and treatments are involved? How does this treatment differ from the existing standard treatment?
+ What is likely to happen, with or without, this new treatment?
+ What side effects are likely? What are the side effects of standard treatment? How long will the study last? Is hospitalization required? Are there long-term or follow-up treatments involved?
+ What will it cost? Will insurance cover any of the treatment?
+ What are the other choices, and what are their advantages and disadvantages?

For more information, contact your physician or contact the MD 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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Emotional Side Effects: Section of Behavioral Medicine in Department of Pediatrics Helps Patients and Their Families Cope with Cancer

by Dawn Chalaire

Those who have never experienced cancer might believe that it has a way of crystallizing life: Ordinary problems and frustrations fade from view as conquering the disease becomes the primary focus. Although cancer survivors and their families sometimes come away from the experience with a clearer perspective, the day-to-day stress of dealing with cancer is more likely to magnify problems, even as it robs patients and their families of the ability to solve them.

"Looking back at some of the problems, they seem so stupid now because they kind of resolved themselves over time. But they were such big problems then," recalled [insert name removed] was diagnosed with cancer.

At that time, Donna R. Copeland, Ph.D., chief of the section of Behavioral Medicine in the Department of Pediatrics at The University of Texas M. D. Anderson Cancer Center, invited [insert name removed] to participate in a problem-solving skills training study being conducted at M. D. Anderson and six other institutions across the country. The training program, called "Bright Ideas," teaches mothers of children with cancer the five steps in problem solving: Identify the problem, Define solutions, Evaluate solutions, Act, and See if it works (IDEAS).

Participants in the intervention arm of the randomized controlled study attend a series of eight sessions with a therapist or trainer to learn how to solve their problems. During the sessions, mothers are given worksheets and asked to write down the major difficulties they are facing, beginning with the most important. [insert name removed] said that at the time, she had two "really big" concerns: finding time to sleep and finding a babysitter for her younger son, who was 18 months old.

"From experience, we now realize that people who are dealing with cancer still have the problems that everyone else does," said Dr. Copeland. "We take problem-solving for granted, but it's really quite obvious when someone needs help in that area. What has also been interesting is that there are some women with great problem-solving skills, but they don't necessarily use them when they are under stress because their concern for their children occupies most of their attention."

One arm of the Bright Ideas study is open to Spanish-speaking mothers, and in a third arm of the study, participants are taught problem-solving skills with the help of a CD-ROM version of the program. To see how well they retain the problem-solving skills they were taught and to measure any changes in their emotional state and stress level, the mothers are given depression index and general emotional coping index tests before they start the program and three months later. Researchers hope that learning and applying the problem-solving skills taught in the program will also improve the mothers' parenting skills, which will in turn benefit their children.

"I guess the most surprising thing was the realizations that I realized just how much I actually was doing," [insert name removed] said. "I knew I was tired, and I kept thinking, 'Why am I so tired? Am I stressed? Am I depressed?' Then I thought, 'No wonder I'm tired.' I was trying to do way too much in a day."

[Insert name removed] said that four years after...
participating in the study, she still applies the principles that she learned there. "It just kind of became second nature," she said.

In another study, also funded by the National Institutes of Health, Dr. Copeland and other psychologists in the section of Behavioral Medicine are testing the effects of cognitive remediation in children with attention deficit disorders related to therapy for central nervous system cancers. The cognitive remediation program consists of 20 two-hour intensive training sessions (lasting a total of five to six months) where children are taught exercises and learning strategies to help them improve their attention skills, do their homework, take tests, and become more organized. The children also receive cognitive behavioral therapy to promote learning and boost their self-confidence.

"It's very stressful for these children, especially those who have a severe deficit," Dr. Copeland said, "to go to school and realize that they are behind or to realize that their academic skills are not what they used to be."

The primary goals of the program are to improve attention and memory, and the researchers hope that these will in turn improve the children's academic performance, school behavior, and self-esteem. As in the maternal study, the children are given tests before and after participating in the training program to evaluate the efficacy of the program. Children who complete the program are evaluated again six months later to assess the stability of their skill improvements.

Another goal of both the maternal problem-solving and cognitive remediation studies is to help the parents become better advocates for their children at school. "We also work very closely with the parents and teachers to inform them about what we're doing and ways that they can duplicate that in the classroom and at home," Dr. Copeland said. "Unless all of this generalizes to the larger part of their lives, it's not going to be very useful."

Dr. Copeland and her colleagues hope to extend both studies to other groups, such as Spanish-speaking families, and would like to investigate the two programs as part of a single study. The maternal problem-solving program is currently limited to mothers of newly diagnosed patients, but they also hope to eventually offer it to mothers of children who have already begun treatment and to mothers whose children have died. Other plans include offering problem-solving skills training to adolescents and children and testing the program's effectiveness in mothers who participate with a spouse or partner.

In addition to conducting research, the section of Behavioral Medicine, which includes psychologists, social workers, child-life specialists, and educational workers, offers clinical programs to help pediatric patients and their families reduce stress by focusing on their cognitive, emotional, and physical needs. Some of the more common manifestations of stress seen in pediatric patients and their parents are disorganization, an inability to sleep, and anxiety.

"One of the most distressing things a human being can go through is having one of their children seriously ill. If the child dies, to me there's nothing worse that can happen to a person. Because not only are you missing that child, but you are feeling guilty because you haven't performed a basic parental function—protecting that child. This may not be realistic, but parents still feel that way," Dr. Copeland said.

Dr. Copeland and other psychologists in the section of Behavioral Medicine provide marital and family counseling, psychotherapy, and hypnosis and relaxation imagery to patients and their families. "Many people are skittish of help from a psychologist," Dr. Copeland said, "so you have to win their confidence and let them know that the way that psychotherapy works is supportive, not critical. Most of the time, they become open to it and find it very helpful. Occasionally, that is not the case, and that is where it is also helpful to have a larger team. Other staff members can fill in because families may be more receptive to a social worker or child-life specialist than to a psychologist."

Social workers in the section of Behavioral Medicine work mostly with the parents, counseling, helping with their finances and housing, and periodically hosting a dinner out so that they can socialize and spend time away from the hospital. Parents can also participate in support groups, a prayer group, exercise programs, and arts and crafts. Quarterly memorial services are held for patients, family members, and staff, and bereavement counseling is offered to family members of patients who have died. Many of these and other programs in the Section of Behavioral Medicine are funded by M. D. Anderson's Children's Art Project and the Pi Beta Phi Children's Enrichment Program.

According to Dr. Copeland, educational staff members can help reduce a child's stress by helping them maintain their educational course. The child-life specialists also play a critical role in stress reduction by supporting the children during medical procedures and in the playrooms and offering special activities, such as arts and crafts.

"I've come to realize," said Dr. Copeland, "that engaging in creative arts is one of the best stress reducers that there is. It's wonderful for coping. The children get lost in their drawings; they often express in their writings, their drawings, and their music some of the things that are hard to say or that they're not likely to say in a normal conversation."

Besides being therapeutic for the children, art can sometimes give the staff clues to a child's emotional state. "There have been times when I have seen some artwork, and I knew that the child needed special help," Dr. Copeland said. "It gives you a little window into their lives and how they function."

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**FOR MORE INFORMATION, contact Dr. Copeland at (713) 792-6635.**
Where Patient Care and Research Meet

Leonard A. Zwelling, M.D., M.B.A.
Vice President for Research Administration

In clinical research, caring for the patient and performing research are one and the same. Physicians who conduct clinical trials do so because they believe that the "research" care they are giving is the best possible option for their patients—better than even the best standard care.

But in this new world of genetic discoveries and gene therapy, how do we continue to provide excellent clinical research while assuring our patients and the federal regulatory bodies that our clinical investigations are ethical and as safe as possible?

At M. D. Anderson, we take this obligation very seriously. We have established a system of checks and balances that has been approved by the Office of Human Research Protection (OHRP), the federal regulatory body that sanctions human subject research.

First, all proposals or plans for clinical research, called protocols, must emanate from the faculty at M. D. Anderson and go through our review process, which is supported by the Office of Protocol Research within the Office of Research Administration.

Every protocol that is submitted to the Office of Protocol Research is immediately registered in our own Protocol Data Management System, which tracks all clinical research at M. D. Anderson.

Each protocol is then evaluated by clinical investigators, radiologists, pathologists, pharmacists, biostatisticians, and nurses, who evaluate the protocols and submit written reviews. The Clinical Research Committee meets twice monthly, and the Psychosocial, Behavioral, and Health Services Research Committee meets monthly with the principal investigators to discuss the protocols before approving or disapproving of them. Often, the committees suggest modifications to the protocols before they are approved.

The approved protocols are then sent to the Institutional Review Board (IRB), a federally mandated body that reviews all proposed research involving human subjects for patient protection and ethical issues. Unlike the other committees, which consist mainly of faculty and staff from M. D. Anderson, the IRB must also include members of the community. The focus of the IRB's attention is the informed consent document, which explains to prospective participants the details, risks, and benefits of participation in a clinical trial. The IRB discusses the details of each protocol and may also recommend modifications.

Finally, every patient who consents to enter a clinical trial is registered in the Protocol Data Management System, which allows each investigator to easily track the progress of his or her trial and allows our office to audit the progress electronically.

This multistep system of peer-review and quality control assures all patients who consent to enter one of our trials that the therapy they will be receiving is the best, safest, and most ethical clinical research care available.
CLINICAL PRACTICE GUIDELINES
Quarterly Supplement to OncoLog
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About These Clinical Practice Guidelines

These guidelines may assist in the diagnostic evaluation of patients with clinical symptoms or positive screening tests (if such testing exists). The clinician is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care.

M.D. Anderson Cancer Center's Practice Guidelines are continually updated as new information becomes available and are being expanded to include the entire spectrum of cancer management. New guidelines for screening and diagnosis are currently under development. Access the most current version of all M.D. Anderson Practice Guidelines from M.D. Anderson's Home Page at http://www.mdanderson.org.

Continuing Medical Education:
An expanded version of these materials with CME category I credit is available on the Internet. Access Practice Guidelines from M.D. Anderson's Home Page at http://www.mdanderson.org.

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CLINICAL DISCUSSION:
Small Cell Lung Cancer

Scope of This Guideline

This guideline addresses the diagnosis, evaluation, and treatment of small cell lung cancer (SCLC). The four main histologic types of lung cancer include squamous cell carcinoma, adenocarcinoma, large cell (anaplastic) carcinoma, and small cell carcinoma. The biological behavior of small cell carcinomas differs significantly from the non-small cell types, which are addressed in a separate guideline. These and practice guidelines for other types of cancer are currently available on our Web site.

Synopsis & Highlights

Diagnosis and Initial Evaluation
After a diagnosis of small cell lung cancer has been confirmed by histology of specimens obtained via bronchoscopy or by cytologic sputum or fine-needle aspiration, specimen analysis, evaluation and staging should proceed without delay, particularly to identify patients in whom lymph node involvement has not developed. “Limited-stage disease is curable,” says Dr. Fossella, “but this is a very aggressive cancer, and we find that once there is nodal involvement, disease is usually widespread.”

Therefore, the initial evaluation is aimed at staging and assessing the extent of disease, as these factors not only determine treatment decisions but also direct further assessment. For patients found to have extensive disease, further assessment tests are not necessary unless symptoms are present; such tests then may include a bone scan or CT scan of the brain to determine the location and extent of metastases for palliative radiotherapy (XRT). Those patients whose disease initially appears limited to the thorax should be further assessed by CT scan of the brain, a bone scan, bone marrow biopsy, and cytologic evaluation of pleural effusion by thoracentesis.

(Continued on next page)
Initial Treatment

Initial treatment decisions are based on stage and extent of disease. Patients with limited-stage disease can be considered for aggressive treatment measures with a curative intent. Patients with solitary nodules and no lymph node involvement may be candidates for surgical resection followed by chemotherapy and, if in otherwise good health, should be further assessed with pulmonary function testing and mediastinoscopy to determine surgical operability.

Those whose disease is not solitary but is still considered limited may be successfully treated with chemotherapy and XRT. Patients in otherwise good health should be considered for accelerated and/or concurrent therapy with these modalities, while those less able to tolerate aggressive treatment may be more appropriately managed with a sequential treatment regime, starting with chemotherapy followed by XRT.

For those patients found to have extensive disease, treatment decisions are aimed at prolonging survival and enhancing quality of life. Chemotherapy is the mainstay of therapy for extensive-stage disease. It is employed along with XRT to palliate symptoms arising from metastases, most notably in this disease to the brain and spinal cord, and also bone pain and symptoms associated with obstruction or invasion of chest structures. The particular agents and regimen chosen are dependent upon the patient's general condition and tolerance.

Response Assessment and Further Treatment

For patients receiving definitive treatment, decisions about adjuvant therapy are guided by the response to initial therapy, so a thorough assessment is appropriate in the posttreatment setting. Patients whose disease has progressed in spite of initial treatment should be provided with supportive care and palliative measures.

Those patients whose disease is judged to have displayed a complete or major response should be considered for prophylactic cranial XRT for occult brain metastases. "While lesions may not be obvious, it appears that without prophylactic cranial XRT, in approximately 80% of these patients brain metastases will develop, including occult metastases within two years," says Dr. Komaki. However, she also recommends that neurosurgical testing be conducted first; as many as 85% of patients with small cell lung cancer present with some cognitive deficiency that may be so subtle as to escape observation.

(Continued on back page)
More about Concurrent Chemotherapy and Radiation

In a recent study at M. D. Anderson, patients were given an accelerated regimen in which, instead of XRT once a day (five treatments/week) for five weeks, they received treatments twice a day (10 treatments/week) for three weeks. Four cycles of chemotherapy using etoposide and cisplatin were given, the first cycle starting concurrently with XRT and the remaining three cycles at its conclusion. In approximately 60% of these patients, disease response was major; and there was a significant increase in 5-year survival rates: 28% compared with 16% on once-a-day regimens. According to Dr. Komaki, patients in the study tolerated the treatment very well, and this is now a standard of care at M. D. Anderson for patients who have limited-stage small cell lung cancer. She emphasizes, however, that this is an aggressive regimen for aggressive disease and while effective, she does not consider it feasible unless supportive care is available.

Current studies at M. D. Anderson are investigating the use of the accelerated (twice daily) XRT regimen with concurrent chemotherapy combinations. The addition of CPT-11 has shown promising results among patients with extensive disease and will be tried in patients with limited-stage small cell lung cancer before and after accelerated XRT with concurrent cisplatin and etoposide.

Screening and Early Detection

The dilemma of lung cancer is that while very early stage disease is curable, most cases are advanced by the time they are detected, and there is no effective screening recommendation that can be feasibly employed in asymptomatic populations. Dr. Komaki and Dr. Margaret Spitz of M. D. Anderson's Department of Epidemiology are conducting an investigation into mutagen sensitivity of lymphocytes to radiation and chemotherapy as an indicator of genetic sensitivity to normal tissue toxicities and carcinogenesis, which may lead to ways to target patients for screening.

Prevention and chemoprevention will continue to be areas of strong research and clinical focus in this disease.


References & Suggested Reading

