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4
Protocols
Clinical trials for patients with bladder cancer are featured.

Compass
Quarterly Supplement
Guidelines discuss the treatment of lymphoma.

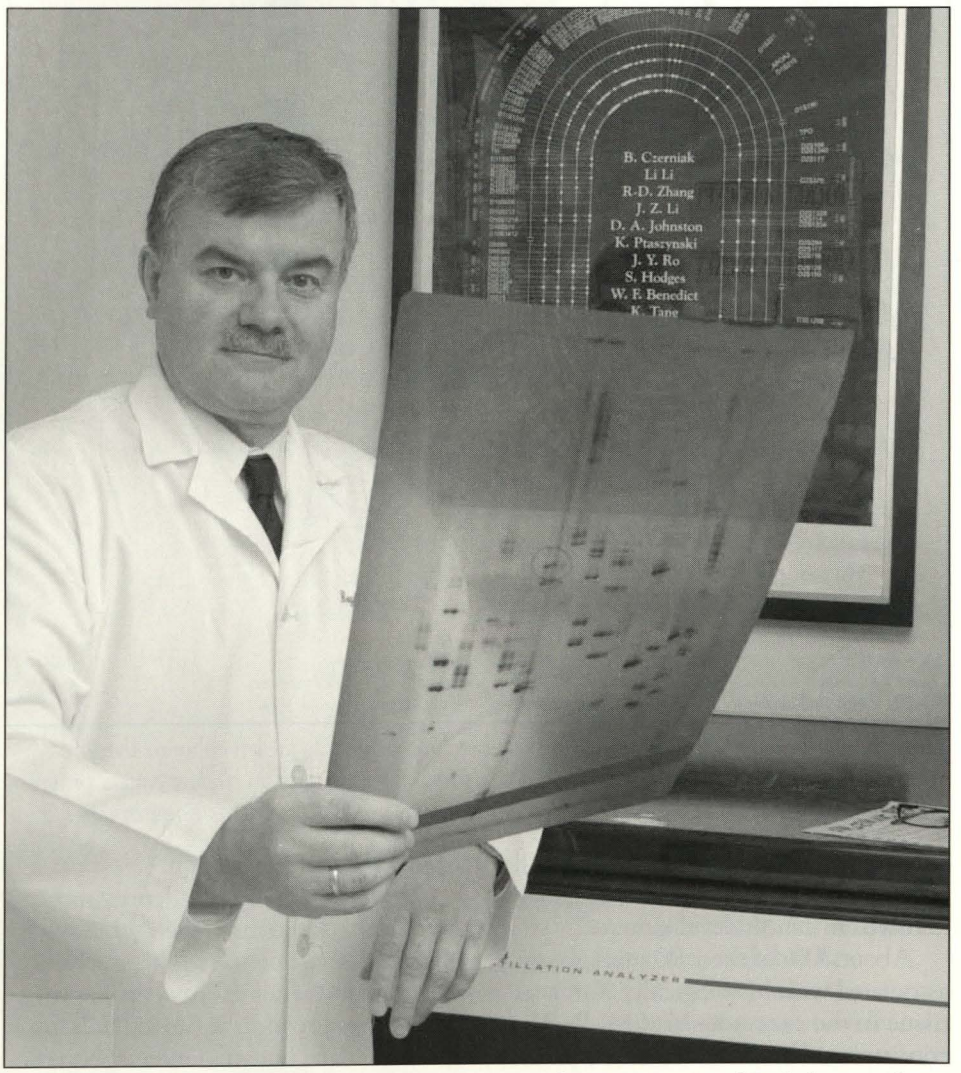
6
A Team Effort
M. D. Anderson nurtures relationships with community physicians.

REPORT TO PHYSICIANS

JUNE 2001 Vol. 46, No. 6

OncoLog

Bladder Cancer Genetic Mapping Effort Builds on Human Genome Project



Dr. Bogdan Czerniak, *an associate professor in the Department of Pathology, and his colleagues are using histologic studies and genetic mapping to identify target genes that may be markers of bladder cancer in its very earliest stages.*

by Kathryn L. Hale

While others waited to see what the Human Genome Project would reveal, Bogdan Czerniak, M.D., Ph.D., a pathologist at The University of Texas M. D. Anderson Cancer Center, had already found an application for it.

Under Dr. Czerniak's direction, a collaborative study now under way at M. D. Anderson and other Texas Medical Center institutions is combining clinicopathologic information from patients with bladder cancer with Human Genome Project data to create a unique genetic map of the disease—a map that researchers hope will lead them to the prevention and earlier detection of bladder cancer.

Like many other solid tumors, bladder cancer has proved a challenge to clinicians. Despite continual refine-

(Continued on **next page***)*

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Bladder Cancer

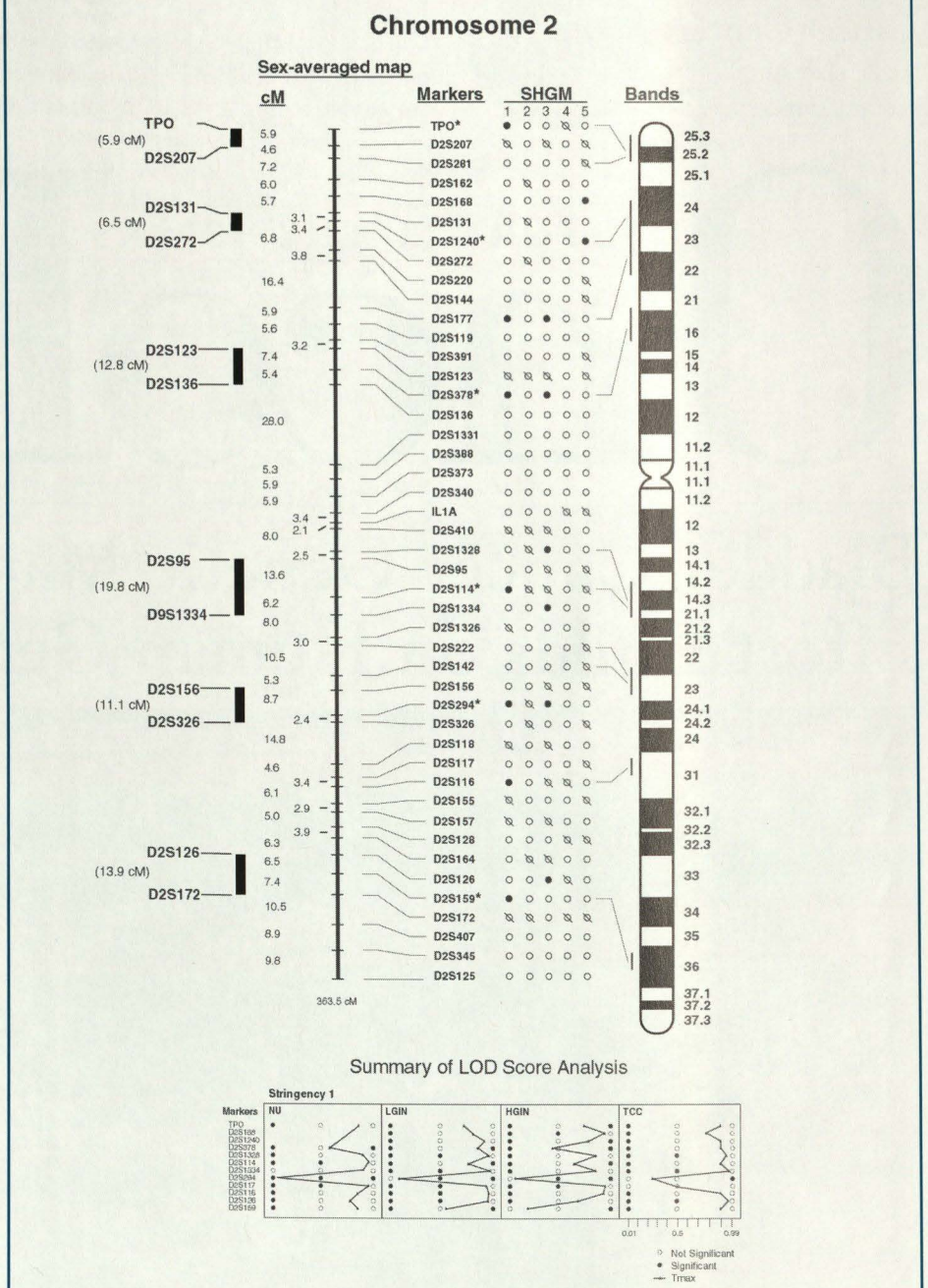
(*Continued from* **page 1**)

ments in treatment strategies, mortality rates from the disease have remained fairly stable over the years. Patients whose disease is detected and treated early tend to have a better chance of achieving remission and living longer than patients whose cancer is advanced by the time it is diagnosed. The emphasis in cancer research, therefore, is not only improving therapies but also improving prevention and early detection strategies.

These strategies have focused largely on exploiting the stepwise progression of neoplastic changes typical of solid tumors. In the progression of tissue from normal to frankly neoplastic are a number of predictable microscopic precancerous changes detectable by histologic studies. It makes sense that once these changes are recognized, they become targets for interventions that could stop the cancerous progression at that point. Some now believe, however, that even these microscopic precancerous changes represent a point too far along in the progression to stop the cancer from developing. Markers of earlier changes are needed, and Dr. Czerniak is looking for them.

Combining histologic and genetic mapping

Dr. Czerniak and his team began by mapping the histologic changes associated with bladder cancer. They took multiple bladder wall samples from a series of patients with bladder cancer and precisely mapped the locations of various preneoplastic cell changes from mild dysplasia to carcinoma in situ. They then analyzed DNA from these samples and, by using known genetic markers, painstakingly searched, chromosome by chromosome, for loci of allelic deletion (a potential genetic precursor of cancer) using now-standard polymerase chain reaction amplification and high-resolution gel techniques. Correlation of this DNA analysis with the "whole organ" histologic mapping identified which of these loci were associated geographically with cancerous tissue changes. Said Dr. Czerniak, "This allowed us to narrow down our list of loci of interest from hundreds to about 90 and yielded a preliminary genetic map of bladder cancer. But these loci were only rough estimates of the exact genes involved in cancer development."



Abbreviations: cM = centimorgan; SHGM = superimposed histologic and genetic maps; LOD = logarithms of odds; NU = normal urothelium; LGIN = low-grade intraurothelial neoplasia; HGIN = high-grade intraurothelial neoplasia; TCC= transitional cell carcinoma.

This map shows the minimally deleted regions on chromosome 2 (far left column) that are involved in the progression of bladder neoplasia. Genome-wide data on bladder cancer progression can be obtained from the Web site www.mdanderson.org/departments/genomemaps.

About 30% of these 90 markers are associated with histologically normal tissue in the cancerous bladder. Besides confirming that genetic changes precede histologic changes in the development of tumors, this yielded a potential set of targets for very early intervention in bladder cancer prevention.

The next step was to identify more precisely the regions of DNA that were altered in these cancers. This is where the Human Genome Project came in. Under the direction of Steven Scherer, Ph.D., of the Human Genome Sequencing Center at Baylor College of Medicine, the "physical map" of human DNA forged by the Human Genome

Project—which comprised genetic sequences of a series of overlapping DNA fragments anchored by known hypervariable markers—was combined with the preliminary genetic map generated in Dr. Czerniak's lab, and the genetic sequences associated with the loci of interest were identified.

"This project, this opportunity, would not exist without the Human Genome Project," asserted Dr. Czerniak. "We are definitely following in its footsteps." The project, which is part of the nearly $10 million Specialized Programs for Research Excellence (SPORE) grant for bladder cancer recently awarded to M. D. Anderson, is a natural extension of the massive Human Genome Project, which is nearly complete. Dr. Scherer said, "This project is a clear demonstration that the Human Genome Project is not an ending but a beginning. It is providing basic tools that can be applied to solve any genetic problem."

Using microarray technology to speed identification of target genes

Defining the associated genetic sequences was a significant achievement, but the sequences themselves are not exact enough for clinical application. Only the specific altered sequences can serve as markers of disease, and further analysis was necessary to pinpoint these target genes. The process of locating specific genes among larger sequences is a laborious one. However, a relatively new technology called microarray analysis has emerged to hasten, if not simplify, this process.

Microarray analysis uses complex hybridization techniques to compare patient DNA with clones generated from Human Genome Project sequencing data. This allows very precise identification of specific genetic sequences that have been lost or altered. Many fragments can be analyzed at one time, telescoping the time needed to generate gene targets. Using DNA fragments supplied by Dr. Czerniak's lab, a group at the Human Genetics Center of The University of Texas School of Public Health led by Li Jin, Ph.D., processes the microarrays. At first glance, Dr. Li, a population geneticist, may seem an odd choice to run this arm of the project, but he said that when Dr. Czerniak approached him three years ago with his idea for analyzing large numbers of DNA samples, "I got the link right away. For this project, I treat populations of cells just like they were populations of humans."

Said Dr. Czerniak, "The microarray technique is easy to explain but technically difficult to implement. It actually maps the target genes from very small DNA fragments." Although microarray technology is gaining a foothold in genetics research, it is still very much in development. Recalled Dr. Li, "The application had to be customized, which meant both constructing the hardware and writing the software. It took nearly two years to develop and has been operational for almost a year. It was very much a trial-and-error process, and we nearly gave up a few times." Added Dr. Czerniak, "Only in the past few months have we been able to process the number of samples we need to process. We are now generating huge amounts of usable data. Our knowledge is exploding, and we're just getting started." The final step in the process is confirmation of the microarray findings by fluorescence in situ hybridization back at M. D. Anderson.

Testing preliminary markers

What does the team plan to do with the target genes they have identified? Dr. Czerniak's lab has received almost $2.3 million from the Early Detection Network, a National Cancer Institute-sponsored network of laboratories that cooperate to identify markers for early cancer detection. As his team identifies target genes, other labs in the network will validate their applicability as markers in the clinical setting. Said Dr. Czerniak, "The basic objective of the project is to move cancer detection from the clinical to the preclinical or occult, histologically undetectable phases of cancer progression and to extend this capability to a number of different cancers. We want to learn how to identify these cancers on the molecular level and use that knowledge to develop novel concepts of cancer prevention."

He continued, "Every lab in the Early Detection Network is using its own unique approach. No one else is doing exactly what we are doing. Obviously, we think this approach will get us to our ultimate goal, which is simple, noninvasive screening tests that will identify cancers in their very earliest stages." Bladder cancer is an ideal candidate for such tests because the bladder is a relatively accessible organ; moreover, urine is the ideal medium for noninvasive testing. Previous tests have indicated that loci of allelic deletion are detectable in the urine of at least some patients with bladder cancer. Dr. Czerniak hopes that eventually his work will lead to the development of tests that are both practical for screening large groups of people and reliable in detecting early bladder cancers.

Preliminary clinical trials are already under way. Seven regional markers of bladder cancer identified in the preliminary phase of Dr. Czerniak's project are being used in a trial funded by the SPORE grant to test chemopreventive strategies for preventing recurrences in patients who have been treated for bladder cancer and are without disease. The effectiveness of the seven markers in detecting early recurrences is being examined. "These seven markers were among the most consistent across all patients tested. More markers will be added to the study as they are developed," reported Dr. Czerniak. "The overall goal is to identify at least five markers with good clinical applicability."

Dr. Czerniak is confident that the research strategy he is helping to develop will eventually provide a key to understanding the evolution of genetic alterations in the progression of neoplastic disease. He reacts with consternation when asked whether the project is too big, too complex. "Cancer is a form of life," he counters. "Do not expect it to be simple." ●

FOR MORE INFORMATION, *contact Dr. Czerniak at (713) 794-1025.*

See page 4 for bladder cancer protocols.

Clinical Trials for Bladder Cancer

Clinical trials in progress at The University of Texas M. D. Anderson Cancer Center include the following for patients with cancers and precancers of the bladder and urothelium.

- Randomized chemoprevention trial with fenretinide (4-HPR) in superficial bladder cancer (ID95-236). *Physician: H. Barton Grossman, M.D.*

  Patients in this phase III trial must have solitary or multifocal superficial transitional cell carcinoma of the bladder that is either newly diagnosed or secondary in patients who have been primary tumor–free for more than a year. Newly diagnosed bladder tumors must have been resected less than four weeks prior to study entry. Women must not be pregnant at the time of enrollment and must comply with mandatory contraceptive measures during the trial and for one year after termination of the drug.

- Methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) in organ-confined bladder cancer based on p53 status (URL98-141). *Physician: Colin Dinney, M.D.*

  Patients with potentially curable, organ-confined bladder cancer are eligible for this multicenter phase III trial of chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). Patients must register for the trial within nine weeks of a radical cystectomy and bilateral pelvic lymphadenectomy and must not have received any prior systemic chemotherapy or pelvic irradiation.

- Phase II surgical consolidation for subdiaphragmatic retroperitoneal and pelvic lymph node metastases following response to chemotherapy in patients with transitional cell carcinoma of the bladder and node-only disease (ID96-193). *Physician: Louis Pisters, M.D.*

  Patients with histologic proof of predominantly transitional cell carcinoma of the bladder and histologic proof of nodal disease may enroll if they have a life expectancy of more than six months. Patients are excluded if they have local soft tissue recurrence or evidence of distant metastasis in the bone, lungs, viscera, or brain or nodes outside the subdiaphragmatic retroperitoneum or the pelvis. This inpatient surgical procedure requires a five- to seven-day stay in Houston with follow-up visits every three months thereafter.

- Intravesical AD-32 treatment of superficial bladder cancer characterized on the basis of the tumor markers p53 and pRb (ID97-038). *Physician: Colin Dinney, M.D.*

  Patients with recurrent stage Ta or T1 transitional cell carcinoma, newly diagnosed multifocal transitional cell carcinoma, or stage T1 transitional cell carcinoma are eligible. Participants must have no evidence of upper tract (ureter or renal pelvic) transitional cell carcinoma. Previous treatment with intravesical AD-32 or with any intravenously administered systemic chemotherapy for bladder cancer is not allowed. Patients who are being treated with other chemotherapeutic agents, biological response modifiers, radiation therapy, or hormonal therapy or who are planning to receive such therapy during the study period will not be eligible.

- A randomized multicenter phase III trial evaluating the efficacy and safety of the BCI immune activator versus doxorubicin in BCG-refractory or BCG-intolerant patients with carcinoma in situ with or without resected superficial papillary bladder cancer (URL99-009). *Physician: H. Barton Grossman, M.D.*

  Participants in this outpatient protocol must have carcinoma in situ of the bladder that has not been treated with intravesical therapy in the four weeks prior to enrollment, radiation therapy in the four months prior to enrollment, or cystectomy. Patients must not have been previously treated with doxorubicin and may not be treated concurrently with any chemotherapeutic drug during the trial. To be eligible, patients must also have disease refractory to or be intolerant of BCG.

- A phase I trial of intravesical adenovirus p53 treatment in locally advanced and metastatic bladder cancer (DM96-172). *Physician: Lance Pagliaro, M.D.*

  Enrollment criteria include histologically confirmed transitional cell carcinoma of the bladder with muscle invasion or lamina propria invasion, unresectable local-regional disease or asymptomatic distant visceral metastases, bidimensionally measurable disease, and a life expectancy of more than 12 weeks. Patients must be HIV-negative and must not have received any prior gene therapy.

- A randomized phase II selection trial of four chemotherapy regimens in urothelial cancer (ID99-393). *Physician: Randall Millikan, M.D., Ph.D.*

  Eligible patients must have histologic proof of metastatic or locally unresectable predominantly transitional cell carcinoma of the urothelium. Participants must also have a life expectancy of at least nine months based on comorbidity and at least eight weeks based on the natural history of their cancer. Exclusion criteria include a clinical history of heart disease and pelvic irradiation in the six weeks prior to study enrollment.

- Phase II trial of ifosfamide and doxorubicin alternating with VP-16 and cisplatin for small cell carcinoma of the urothelium (DM00-039). *Physician: Randall Millikan, M.D., Ph.D.*

  Patients with histologically confirmed small cell carcinoma of the urothelium will be considered for this inpatient trial requiring an initial 21-day stay in Houston and subsequent follow-up every six weeks. No clinically or radiographically measurable disease is needed for patients with bladder-only cancer. For those with metastatic disease, at least one site must be measurable. Patients must not have been previously treated for metastatic disease but may have been treated with chemotherapy in some instances.

- Phase II evaluation of bladder preservation in T0, Ta, Tis, and T1 bladder cancer after chemotherapy (URL96-005). *Physician: Colin Dinney, M.D.*

  This trial is designed for patients with invasive bladder cancer that has responded well to systemic chemotherapy. Patients must have a documented complete response in all metastatic sites and normal or minimal bladder-wall thickening in the primary site. Those with urothelial carcinoma of the renal pelvis, ureter, urethra, or prostate will be excluded, as will those treated for a prior malignancy (unless they have been disease-free for at least five years). ●

FOR MORE INFORMATION *about these clinical trials, physicians or patients may call the M. D. Anderson Information Line. Those within the United States should call (800) 392-1611; those in Houston or outside the United States should call (713) 792-6161. Visit the M. D. Anderson Cancer Center clinical trials Web site at http://www.clinicaltrials.org for a broader listing of treatment research protocols.*

HOUSE•CALL

Overcoming Barriers to Cancer Screening for Men

Early detection of cancer has saved thousands of lives, yet we all have a tendency to put off getting the recommended cancer screening tests. Societal pressures can make it especially difficult for men to take part in testing and follow cancer screening guidelines.

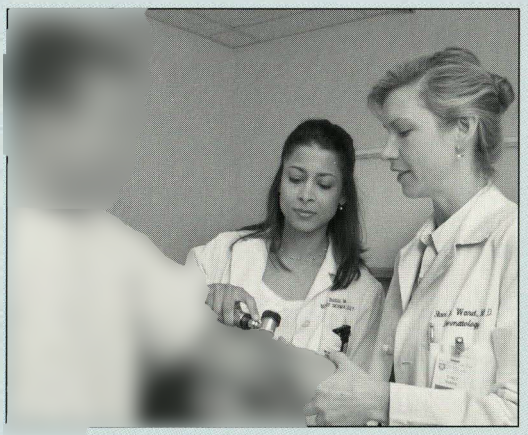
In general, men are less likely than women to participate in important preventive health activities, according to Leslie R. Schover, Ph.D., an associate professor in the Department of Behavioral Science at M. D. Anderson Cancer Center. "Men in our culture are brought up with the male stereotype to be strong, uncomplaining, and tough," said Dr. Schover. "For many men, a checkup is a sign of weakness. They may even wait until a health emergency to see a doctor."

Bernard Levin, M.D., vice president for cancer prevention at M. D. Anderson, said that some men are embarrassed by examinations of the rectum, or they fear the possible physical discomfort of the tests. They may also worry that surgery for pelvic cancer, such as prostate or colorectal cancer, could cause sexual dysfunction. (This is a valid concern; however, many men are able to stay sexually active after these treatments, either because they recover good sexual function or with the help of medical treatments.)

The American Cancer Society estimates that if all Americans had the recommended early detection testing, the five-year survival rate for people with colorectal, prostate, testicular, mouth, and skin cancers would increase to 90% or higher. In addition, the treatment for earlier-stage cancers is often less aggressive and more successful than that for advanced cancers. The following screening exams are recommended for men.

If you or someone you know is reluctant to get screened for cancer, try the following suggestions:

1. Read and understand the specific benefits of cancer screening.
2. Check out your insurance benefits, or take advantage of free cancer screenings.
3. Make an appointment to see your physician and discuss your screening options.



■ Prostate screening

M. D. Anderson recommends an annual digital rectal examination (a health professional inserts a gloved finger into the rectum and feels the prostate gland for abnormalities) and a prostate-specific antigen blood test for men ages 50 to 70 who have a life expectancy of at least 10 years and who have been counseled and understand the risks of screening.

■ Colorectal screening

Starting at age 50, men should have both a yearly fecal occult blood test, which checks for signs of blood in the stool, and a flexible sigmoidoscopy, an exam of the rectum and lower colon using a lighted instrument, every five years. Done at home, the fecal occult blood test requires the client to take small samples of three consecutive bowel movements and then mail the results to a lab. Other options for colorectal screening are a colonoscopy, an exam of the rectum and entire colon with a lighted instrument, every 10 years or a double-contrast barium enema every five years. For the latter test, a series of x-rays are taken after the patient is given an enema with a barium solution that outlines the colon and rectum on the x-rays.

■ Skin exams

Beginning at age 18, men should check for a mole or freckle that has jagged borders, color that isn't uniform, or a diameter larger than a pencil eraser. These changes or any new, colored skin growth should be reported to a physician for further testing. Skin checks should be part of a regular physical given by a doctor.

These simple exams can save a man's life—provided he takes advantage of them. For more information about cancer screening and prevention, call the M. D. Anderson Cancer Prevention Center at **(800) 438-6434**. ●

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

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

✆ **(713) 792-6161** *in Houston and outside the United States.*

June 2001

Keeping in Touch: Office of Physician Relations Builds Partnerships, Maintains Contact with Community Physicians

by Dawn Chalaire

Today, physicians from around the world can refer their patients for treatment at The University of Texas M. D. Anderson Cancer Center without ever setting foot on the campus of the Houston, Texas, facility. But rapid growth at the center—fueled, in part, by an increase in referrals—has been a mixed blessing. While more and more patients are receiving the specialized care that they need, personal contact between community physicians and the institution's faculty is becoming more difficult.

The challenge of providing community doctors with a face to go along with the M. D. Anderson name is being met by the Office of Physician Relations. Through visits by physician relations coordinators, exhibits at major medical meetings, and educational events, representatives of M. D. Anderson and its faculty have the opportunity to meet with community physicians in person to build partnerships that are vital to the center's battle against cancer.

"As a tertiary care center, we are dependent upon referrals from the outside to survive," said Richard J. Babaian, M.D., a professor in the Department of Urology and co-medical director of the Office of Physician Relations. "We have to learn as a group to be more available and responsive to physicians who are helping us take care of patients. We may not be the patient's only doctor. That is where the concept of partnering with them becomes very important."

Lori Lund, *a physician relations coordinator in the Office of Physician Relations, visits with* **Dr. Richard Baltz**, *a medical oncologist and M. D. Anderson Network Physician.*

Photo by Karen Lowery. Reprinted with permission from "Physician Relations Coordinators … A Bridge to Community Physicians"

At M. D. Anderson, 56% of patients—an average of more than 35 per day—are referred by or at the advice of their physicians. Luis Campos, M.D., a medical oncologist and community medical director of the M. D. Anderson Physicians Network, said that he refers patients to M. D. Anderson when their disease calls for treatments that he cannot provide, when a second opinion is needed to establish the diagnosis, or when the patient requests it.

Since 1996, the number of admissions to the institution has risen by 12%, while the number of outpatient visits has risen by 37%. More patients often means longer waits for initial patient appointments and busier faculty members who can be more difficult to get in touch with, said Lewis Foxhall, M.D., associate vice president for health policy and co-medical director of the Office of Physician Relations, which also monitors the referral process and responds to complaints or requests for help.

"Most of the time," Dr. Foxhall said, "the referral process goes smoothly, but one problem is one too many for us. Some of these are really individual issues … so we really have to take them one at a time and try to work out the best solution we can."

According to Lyle Green, assistant vice president for referral development in the Office of Physician Relations, the two issues that are most important to community physicians are patient access and communication. Dr. Campos echoed that assessment, saying that when physicians are attentive to the referring doctor, the referral process is very easy. He added that a lack of integration between the clinic and the business office sometimes creates headaches for patients. "Ideally, the clinical part should be integrated with the financial part, especially for international patients," Dr. Campos said. M. D. Anderson is in fact shifting from a centralized business office and

referral center to business offices and referral centers located within each care center, a move that is expected to streamline the process of making appointments. The institution has also implemented a document management system that automates much of the transcription and feedback process so that reports can be sent to the referring doctors more quickly, efficiently, and consistently.

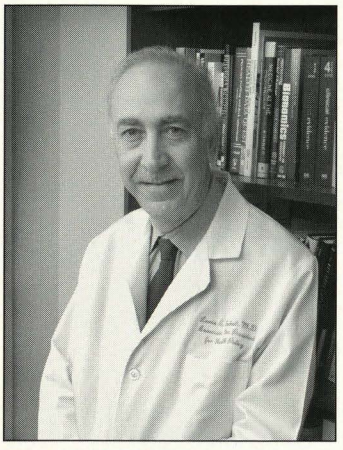
Joseph Kong, M.D., an adjunct associate professor of radiotherapy at M. D. Anderson, who also has a private practice, said that promptness is the most important characteristic of a good referral experience. Dr. Kong said that he prefers to refer patients by phone, and ideally, he would like "to make one phone call and be able to tell the patient when their appointment is before they leave my office."

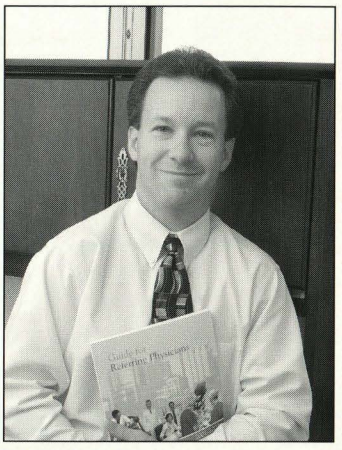
To gauge the success of the referral process, the Office of Physician Relations asks all referring physicians to complete a survey about their experience after each patient referral. Among other questions, the survey asks physicians to rate their level of satisfaction with M. D. Anderson when it comes to the assistance they received in obtaining financial authorization for their patient and the timeliness of feedback about the patient.

"There is also an opportunity for physicians to make suggestions to the faculty about what they might do better or change to make the process more effective," Dr. Foxhall said. "The survey is based on a particular referral, so we can give feedback to the care center that the community doctor was working with."

"Several times a year, we go over referral activity information with the faculty and administrative leadership in each center so they understand their physician referral base," Green added. "We also present feedback information, and we will provide them with quarterly reports on the satisfaction survey."

One way that referring physicians can help the institution keep them informed, Green said, is by reminding patients whom they have directed to call M. D. Anderson for an appointment to provide the referring physician's name and address as the follow-up doctor. Having accurate and complete contact information about a patient's physician is essential to enabling M. D. Anderson's information and document management systems to link the referring physician to the patient record.





Dr. Lewis Foxhall *(left), co-medical director of the Office of Physician Relations, and* **Lyle Green**, *assistant vice president for referral development, work to build partnerships between M. D. Anderson and physicians in the community.*

Besides responding to requests for information and assisting with the referral process, the Office of Physician Relations promotes communication between M. D. Anderson and community physicians through several programs and activities.

Physician relations coordinators meet individually with doctors in their offices in Houston and the surrounding area, answering questions, discussing areas of concern, and sharing with them information about new services, programs, or clinical trials available to them or their patients.

"Because our faculty have limited opportunity to meet with the clinical community physicians on a regular basis, our staff helps to bridge the gap there and serves as a liaison between the institution and the doctors out in the community," Dr. Foxhall said.

The office also works with local hospitals and other interested groups to offer cancer education programs and faculty-led continuing medical education (CME) classes to doctors in the community. Richard Baltz, M.D., a medical oncologist and M. D. Anderson Network Physician, said that he attends CME classes sponsored by M. D. Anderson as often as possible.

"These are very good resources for community oncologists to utilize," Dr. Baltz said.

Representatives from the Office of Physician Relations also attend major medical society meetings, where they meet with physicians in private practice, sharing news from the institution and receiving feedback. Often, faculty members spend time at the exhibit booth, meeting with other physicians and answering questions. The office is exploring opportunities to contact referring physicians in the communities where the meetings are held as a means of establishing personal relationships with physicians outside of the region where office visits are currently made.

Green emphasized that the Office of Physician Relations welcomes calls from physicians and has an oncology nurse on staff to answer specific, clinically oriented questions about clinical trials.

"If community physicians have a problem or an issue they want to talk to us about, or if they need some information about a clinical trial they can't find on our Web site, we would be more than happy to work with them," Dr. Foxhall said. "We want them to be aware that if there is a problem, we really want to hear about it and work with them to correct it." ●

FOR MORE INFORMATION *about the Physician Relations program at M. D. Anderson or to contact a Physician Relations coordinator, please call (713) 792-2202 or (800) 252-0502 or send an e-mail to physicianrelations@mdanderson.org. Community physicians and their office staff are encouraged to visit the Physician Relations Web site at http://www.mdanderson.org/physicianrelations.*

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Staff Publications in June

Below is a partial list of staff publications appearing this month.

Bruera E, Sweeney C, Calder K, Palmer L, Benisch-Tolley S. Patient preferences versus physician perceptions of treatment decisions in cancer care. *J Clin Oncol* 2001;19(11):2883-5.

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CLINICAL PRACTICE GUIDELINES
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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.

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CLINICAL DISCUSSION: Diffuse Large B-Cell Lymphoma

Scope of This Guideline

Non-Hodgkin's lymphoma (NHL) represents as many as 30 biologically different diseases. These entities are currently classified according to the Revised European-American Classification system, although work is currently under way to develop a system that better reflects the clinical behavior and natural history of the various NHL subtypes. Some subtypes of NHL share common diagnostic and treatment elements, and therefore the treatment guidelines for some subtypes of NHL may apply to others. The guideline presented here addresses the evaluation, treatment, and follow-up care of patients who have diffuse large B-cell lymphoma, a clinically aggressive and commonly occurring subtype of NHL. Other NHL subtypes are addressed in separate guidelines, as are those occurring in patients with HIV. Hodgkin's disease is considered a separate category of lymphoma and is also addressed in its own guideline.

Synopsis & Highlights

Overview

Non-Hodgkin's lymphomas are a heterogeneous group of malignancies that usually present in lymphoid tissues (e.g., lymph nodes, spleen, and bone marrow) but can arise in almost any tissue. The most common extranodal sites are the stomach, skin, oropharynx, small intestine, and central nervous system. Their multicentricity and pattern of spread distinguish these neoplasms from Hodgkin's disease: NHL tends to spread early, and widely, in noncontiguous rather than orderly lymphatic patterns. The most important determinant of outcome, however, is not the extent of spread but rather the histological classification. The low-grade histologic subtypes, which include small lymphocytic and follicular lymphomas, tend to have a slow-growing, or indolent, disease course. Relapses are common and may occur after several years. The "curability" of patients with those lymphomas is therefore controversial. Diffuse large B-cell lymphoma, on the other hand, is considered aggressive, and yet paradoxically, approximately half of the patients with this disease subtype are considered curable with standard therapy. This is because the tendency to grow quickly renders the

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disease more responsive to chemotherapy and radiotherapy. If these lymphomas relapse, they tend to do so quickly (within 2 to 3 years).

The treatment approach for diffuse large B-cell lymphoma is multimodal, with combination chemotherapy as the mainstay. Radiotherapy (XRT) is also recommended for patients with localized disease that has responded to chemotherapy and for those who have advanced bulky disease. Peripheral stem cell transplantation is used to treat relapsing or unresponsive disease.

Initial Evaluation

Correct identification of the histologic subclassification is central to the successful treatment of lymphomas. All lymphoma guidelines, therefore, begin with a diagnostic and staging evaluation that includes a careful morphologic examination of lymph node or tumor tissue biopsy samples and in many cases, immunophenotyping and molecular analysis. Close coordination with a hematopathologist experienced in lymphoma is recommended. The biopsy should be excisional; pathologic diagnosis of lymphoma relies on the analysis of architectural alterations, so core needle biopsy and fine-needle aspiration (FNA) may not be adequate. In cases where an excisional biopsy is not possible, a core needle biopsy with two or three samples is preferable to FNA. Optimally, the most clinically significant site should be biopsied and an intact lymph node removed and delivered as a fresh specimen for pathologic examination.

Staging

Once the lymphoma is histologically classified, further staging is appropriate for determining a treatment approach. It is important to evaluate and document the extent of disease, beginning with a thorough history and physical examination. As a leukemic blood phase may occur in some lymphomas, hematologic and bone marrow studies are indicated, which may include histochemical staining, immunophenotyping, cytogenetic analysis, and in some cases, molecular genetics.

Imaging studies may be indicated by physical findings and presentation and may include x-rays, computed tomography (CT), positron emission tomography (PET), and gallium scans, which can be useful in differentiating fibrotic tissue from a viable tumor. The presenting symptoms may indicate additional studies to evaluate disease extent (e.g., bone or gastrointestinal studies).

The Ann Arbor classification system for NHL is based on the location and distribution of lymphatic and non-lymphatic organ involvement. The M. D. Anderson tumor score, like the International Prognostic Index, considers the Ann Arbor stage along with other factors that reflect tumor burden and correlate with prognosis. The tumor score is derived by assigning one point for each of the following conditions:

- a lactate dehydrogenase (LDH) level elevated $\geq$ 10% above normal
- a beta$_2$ microglobulin (B_2M) level $\geq$ 3.0 (i.e., $\geq$ 1.5 times the upper limit of normal)
- a tumor mass $\geq$ 7 cm in maximum dimension
- the presence of secondary systemic ("B") symptoms consisting of unexplained fevers, drenching night sweats, or > 10% weight loss over the preceding 6 months
- Ann Arbor stage III or IV disease

Patients with diffuse large B-cell lymphoma who present with tumor scores of 0 to 2 have a 5-year overall expected survival rate of 60% to 85%; this rate drops to approximately 20% to 40% for those with scores of 3 or higher.

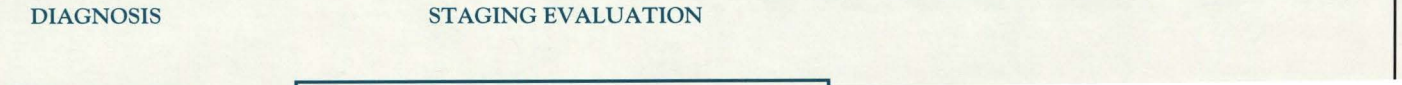
Initial Treatment

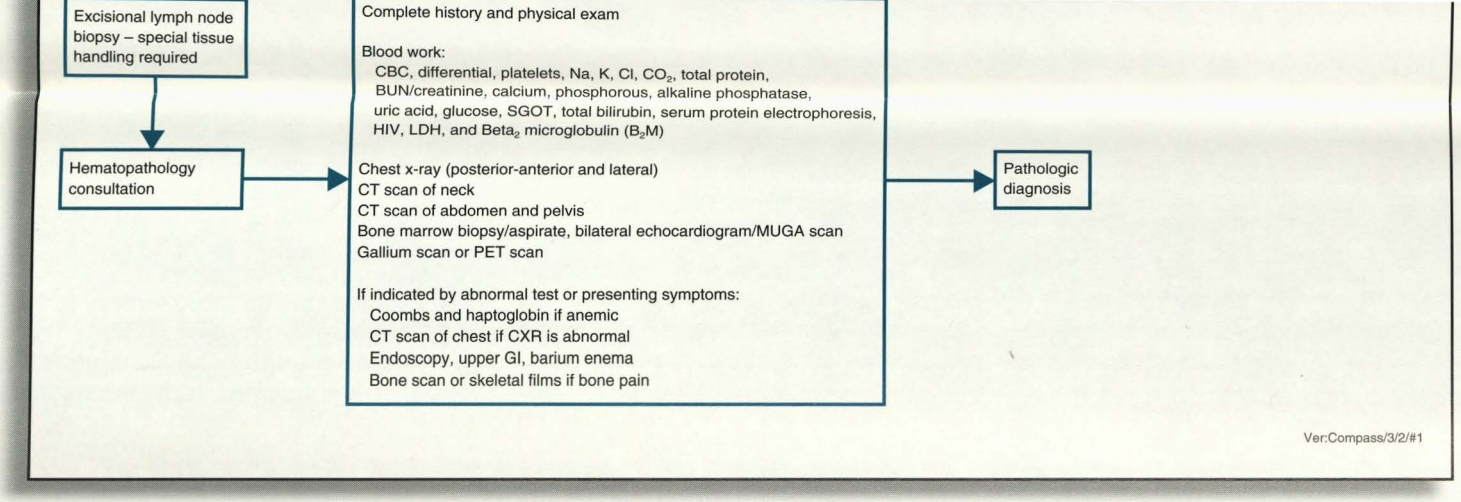
The goal of initial treatment is to achieve a complete remission. According to Dr. Rodriguez, this subtype of NHL has been shown to be a rapidly progressing disease for which the median duration of survival if untreated or unresponsive to treatment is 1 to 2 years. However, long-term disease-free survival and cure have been achieved in a high percentage of patients with a tumor score of 0 to 2 using combination chemotherapy followed by involved-field radiotherapy. Currently, the most widely used chemotherapy regimen is the CHOP regimen, a combination of cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Oncovin), and prednisone. For patients more than 60 years of age, the monoclonal antibody rituximab (Rituxan) is added to this combination (R-CHOP).

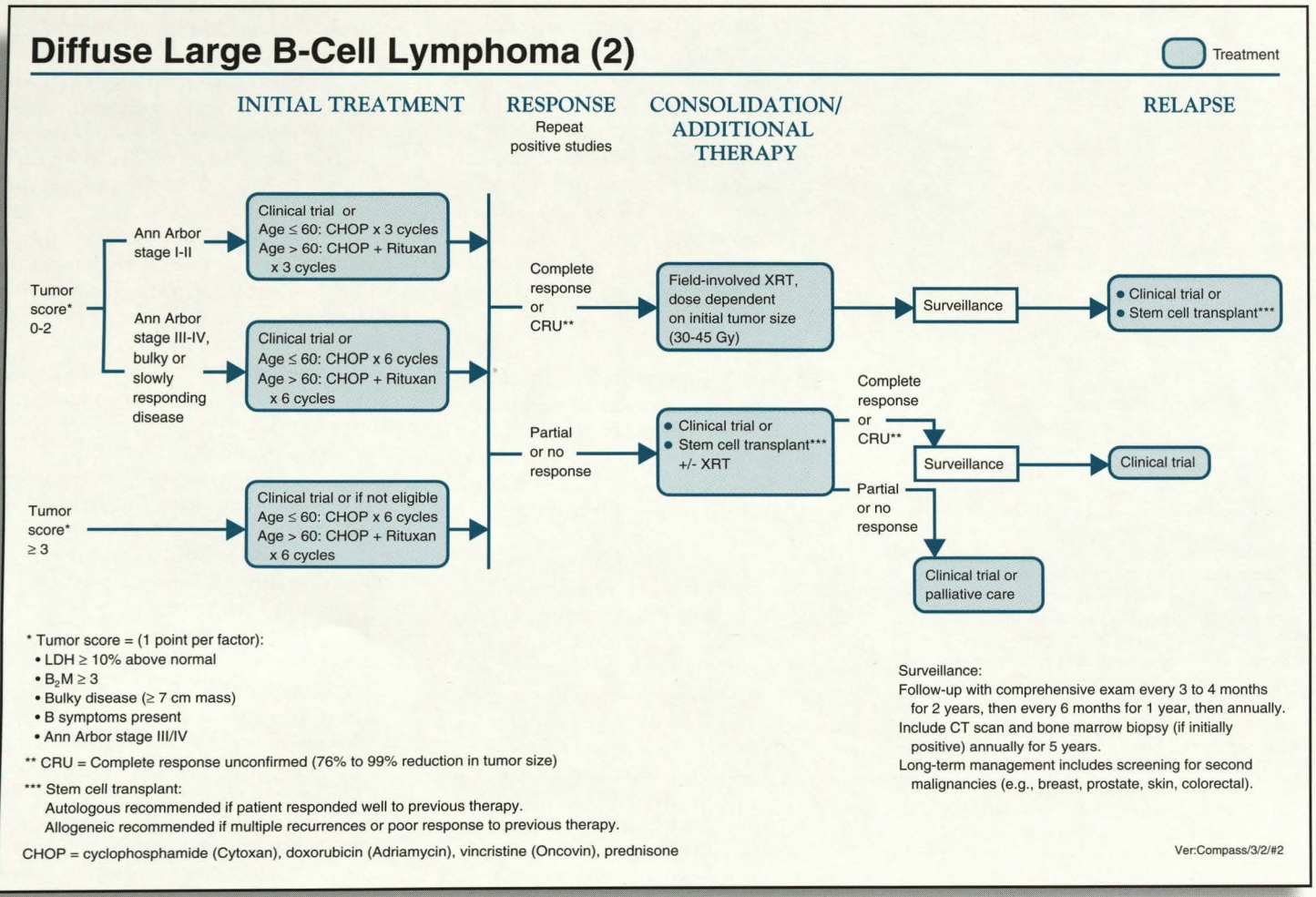
Patients who present with localized disease (tumor score 0 to 2, Ann Arbor stage I-II) are treated with three cycles of CHOP (R-CHOP for patients older than age 60) chemotherapy, followed by a response evaluation in which previously positive tests for tumor presence are repeated. For patients who have a complete response to CHOP or R-CHOP, involved-field XRT is recommended, particularly in localized-stage disease where an abbreviated number of chemotherapy cycles is given. According to Dr. Wilder, the XRT dose is tailored to the size of the tumor *before* chemotherapy: a dose of 30.0-30.6 Gy is used for tumors < 3.5 cm in diameter, 39.6 Gy for tumors 3.5-10.0 cm, and 45.0 Gy for tumors > 10 cm. If the response to CHOP or R-CHOP therapy appears to be incomplete, a gallium scan is indicated, and if the residual mass is found to be gallium-positive, a biopsy is recommended. If the biopsy is positive, indicating persistent active lymphoma, high-dose chemotherapy and a peripheral blood stem cell transplant are recommended; if the biopsy is negative, involved-field XRT is the recommendation.

Patients with a tumor score of 0 to 2 who have bulky disease, stage III-IV disease, or slowly responding tumors are treated initially with six courses of CHOP (or R-CHOP) chemotherapy. This is followed by either XRT or by stem cell transplantation (with or

Lymphoma (All Types): Diagnosis and Staging (1)







M. D. Anderson's Practice Guidelines were developed by multidisciplinary teams of physicians and nurses and are intended to represent evidence-based cancer care with consensus of opinion used secondarily. The core development team for this guideline included Dr. Richard E. Champlin, Dr. Maria A. Rodriguez, and Dr. Richard B. Wilder.

without XRT), depending upon the response, as outlined above.

Patients who present with advanced-stage disease (tumor score ≥ 3) are less likely to be cured with standard therapy and are best treated in clinical trials using new regimens. In one such study at M. D. Anderson (DM95-121), patients are treated with either high-dose chemotherapy and stem cell transplantation or with an aggressive chemotherapy program of three alternating non–cross-resistant chemotherapy regimens.

Relapse

The management of recurrent disease is largely directed by the response to earlier therapy. Other influencing factors are the patient's age and performance status, the extent of recurrent disease, and the duration of remission. Response is assessed on the basis of a clinical examination and a CT scan. A bone marrow aspiration and biopsy is performed only if a previous one was positive or if it is indicated by the appearance of new abnormalities. A complete response (CR) is defined as the complete disappearance of all detectable evidence of disease (clinically and radiographically), including normalization of biochemical abnormalities. An unconfirmed complete response (CRU) is a 76% to 99% regression in tumor size, and a partial response (PR) requires a 50% to 75% decrease in the size of the six largest dominant nodes or nodal masses plus a > 50% regression in splenic and hepatic nodules, with no new sites of disease. Relapse is defined as the appearance of any new lesion or an increase in the size of a previously identified node or lesion by > 50%.

In cases of partial or no response to earlier therapy, treatment with an allogeneic nonmyeloablative peripheral blood stem cell transplant has produced encouraging results. According to Dr. Champlin, this procedure, sometimes called a mini

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transplant, is less toxic than a standard "high-dose" bone marrow transplant. Stem cell transplantation consists of the intravenous administration of stem cells, preceded by high-dose chemotherapy. The main purpose of the prior chemotherapy is to suppress the recipient's immune response to prevent rejection of the transplant, but it also reduces the tumor burden. Allogeneic transplants confer a graft-versus-lymphoma effect in which the donor's immune cells eradicate the lymphoma. Autologous transplantation is less effective but has a lower risk of complications, and therefore it is chosen in favorable cases (first relapse, good response to initial therapy) and in cases where the patient is not able to tolerate the stronger treatment. An allogeneic transplant is recommended in more difficult cases, such as those involving multiple recurrences or poor responses to prior therapies. Clinical trials are highly recommended in this setting.

Surveillance

When an aggressive lymphoma relapses, it usually does so within 2 to 3 years, so frequent follow-up evaluations are recommended after treatment.

The risk of developing a second malignancy is higher for patients who have been treated for NHL, so vigilant screening for other cancers is part of the long-term management of these patients and should include:

- Mammography. Women who have undergone radiotherapy to the breasts should have a baseline mammogram starting at age 40 (or 10 years posttreatment if they were less than 30 years old at the time of irradiation). Mammography should be repeated annually or as needed.
- A prostate-specific antigen test for men beginning at age 50 and repeated annually until age 70
- A baseline colonoscopy, yearly fecal occult blood test, and appropriate work-up for all patients starting at age 50
- Skin examinations for all patients yearly
- A chest x-ray annually
- A urinalysis annually, especially if treated with high-dose cyclophosphamide
- Thyroid function studies for patients who have undergone radiotherapy to the neck

In addition, adult vaccines for influenza, hepatitis, and pneumococcus as recommended by the Centers for Disease Control are indicated, especially for patients who have undergone splenectomy.

Authors' Perspectives

Despite the fairly high cure rate for patients with this subtype of NHL, it is important to develop therapies that are less toxic and more effective. In addition, the ongoing development of immunotherapeutic strategies such as vaccines, DNA antisense molecules, and monoclonal antibodies makes it imperative that we continue to reassess previously held concepts of accepted treatment strategies. For this reason, it is important to consider clinical trials as the preferred choice for all stages and subtypes of NHL.

Find more information about clinical trials and current protocols available at M. D. Anderson at *http://www.mdanderson.org/research/*.

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