Drug Development Program Paves the Way for FDA Approval of New Agents

by Kate Ó Súilleabháin

The Pharmaceutical Development Center (PDC) at The University of Texas M. D. Anderson Cancer Center is a seven-minute drive from the main clinic in Houston, TX. Unobstructed by roadwork crews—a rarity in the ever-growing Texas Medical Center—it is a simple, smoothly paved route that bears no resemblance to the complicated path a new drug must follow from the initial discovery of its anticancer properties in the laboratory to its use in the clinic.

To reap the ultimate reward of drug development—U.S. Food and Drug Administration (FDA) approval of an (Continued on next page)

Dr. Gabriel Lopez-Berestein, a professor in the Department of Bi immuno-therapy and director of the Cancer Therapeutics Discovery Program, examines a Western blot with graduate research assistant Sangeeta Cheema, M.S.
agent for clinical use—a researcher must first test a drug in the laboratory, studying the drug's action in cultured cells to prove its efficacy in vitro. Then, preclinical testing in animal models must show safety and should demonstrate reproducible anticancer effects. To gain permission to study the drug in patients, the researcher must file an Investigational New Drug (IND) application with the FDA. The IND application contains preclinical test data, as well as an institutional review board–approved plan for phase I clinical testing of the agent. The phase I trial, in turn, establishes the safety of the experimental therapy when it is administered at a given dose through a specific route of delivery. Once a safe dose and schedule of administration have been established, the relative anticancer efficacy needs to be determined in phase II trials. Not to be ignored toward the end of this painstaking path are tests to optimize the drug formulation and packaging.

Each step in the arduous process of drug development requires a tremendous amount of time, money, and other resources. At M. D. Anderson, the Cancer Therapeutics Discovery Program (CTDP) was designed to help researchers who have novel ideas take their discoveries to the clinic, said Gabriel Lopez-Berestein, M.D., CTDP director and a professor in the Department of Bioimmunotherapy. (In founding the program three years ago, Dr. Lopez-Berestein drew upon his own experience in obtaining FDA approval for the antifungal agent liposomal amphotericin B, which he shepherded through all stages of development over a 15-year period.)

**CTDP structure and services**

The CTDP has three parts: an awards system to fund various aspects of drug development for individual researchers; a communications and education program that organizes focus groups and retreats for M. D. Anderson faculty, and the PDC, which provides the scientific, laboratory, and regulatory expertise for the preclinical and clinical development of agents with potential to improve cancer therapy. The PDC has assisted more than 50 faculty members since its inception two years ago and is currently engaged in about 12 drug development projects.

Researchers at M. D. Anderson who are investigating new agents can call on the PDC for help at any stage in the drug development process. "We're interested in developing individuals' research, where a person says, 'I've got this really interesting drug, but I'm stuck,'" said Robert Newman, Ph.D., director of the PDC and a professor in the Department of Experimental Therapeutics. "Some faculty members come to us with compounds that are in a very early stage of development. Others are extremely independent and like to develop drugs on their own but need help in a certain area," he said.

The PDC fosters the independent research goals of faculty members by providing highly specialized analytical services. Preclinical testing in animal models with various tumors (performed at M. D. Anderson veterinary facilities in Houston, Bastrop, and Smithville, TX) provides data that show the safety of a compound at various dosages. These data also are needed for the approval and design of clinical trials. At the main campus in Houston, laboratory services include studies that reveal mechanisms of action and antitumor activity in vivo, pharmacokinetic assessments, analytical services, and toxicology testing. In the PDC's pharmacy component, expertise on drug manufacturing, formulation, and packaging is offered.

Although some independent laboratories provide similar resources, having the PDC available in-house offers many benefits to M. D. Anderson and its faculty members. Most important, the PDC provides consultation services that help investigators plan each step in the drug development process. "Outside labs typically do whatever test is requested by the investigator rather than come forward with a total drug development plan like we do," said Timothy Madden, Pharm.D., DABCP, co-director of the PDC. "We actually help investigators understand what needs to be done on the development path."
The Cancer Therapeutics Discovery Program (CTDP) was designed to help researchers who have novel ideas take their discoveries to the clinic.

plant that grows along the U.S. Gulf Coast and in the Mediterranean. The drug’s beneficial effects in people with cancer were first noted in anecdotal stories that originated in Turkey. Development of the extract as an anticancer agent began five years ago. The PDC identified the major constituents of the plant extract and developed working hypotheses of how the plant’s components participated in killing tumor cells.

Research conducted at the PDC supported an IND application, and a successful phase I trial of the extract was recently conducted in the United States. The next step will be to obtain definitive proof of the anticancer efficacy of this novel plant-derived product in phase II trials. Meanwhile, the PDC continues to investigate the drug’s mechanism of action, its effectiveness in combination with standard chemotherapeutic agents, and alternative routes of administration.

Also under development in the PDC is a new use for the benzodiazepine known as midazolam. This drug may be a valuable alternative to opioid therapy for severe, intractable pain or pain syndromes that are unresponsive to opioids. “That’s every bit as beneficial to our patients as some ‘blockbuster’ drugs,” Dr. Newman said.

Midazolam’s analgesic benefits are likely due to its effects on GABA, the major inhibitory neurotransmitter in the central nervous system. The PDC has helped to facilitate preclinical evaluation of a preservative-free midazolam preparation for intrathecal administration in sheep and pig models. These preclinical studies, led by Samuel Hassenkamp, M.D., a professor in the Department of Neurosurgery, and Mary Johansen, Pharm.D., an assistant professor in the Department of Experimental Therapeutics and manager of the PDC, have shown that intrathecal midazolam, delivered via implanted infusion systems, provides significant pain relief without toxicity at doses proposed for human trials. These data will support an IND application to begin clinical testing of intrathecal midazolam in patients with severe cancer pain.

Interinstitutional collaborations

Other PDC efforts involve collaborations with researchers from institutions outside M. D. Anderson. Michael Andreeff, M.D., Ph.D., a professor in the departments of Blood and Marrow Transplantation and Leukemia, and Michael Sporn, M.D., a professor in the departments of Medicine and Pharmacology and Toxicology at Dartmouth Medical School in Hanover, NH, are investigating the unique triterpenoid compound 2-cyano-3,12-dioxyolean-1,9,12-dien-28-oic acid (CDDO) and its methyl ester analogue, CDOD-Me. These compounds have shown activity against various leukemias and other cancers. Studies also suggest the utility of the agents for cancer prevention.

The PDC is working with Drs. Andreeff and Sporn to define the pharmacological properties of these drugs, their overall toxicity profiles, and the most effective doses for clinical study. The data from these studies will be used to support an IND application and to design phase I clinical trials.

Researchers in the PDC and the CTDP point out that the founding of these interactive programs was a formalization of grassroots efforts already being made to fulfill the institution’s mission to cure cancer. “Rather than going out and hiring medicinal chemists, we basically opened our laboratories and volunteered our services,” Dr. Madden said. “We were able to put everything together under one roof, so we were able to offer the expertise that already existed here at M. D. Anderson.”

For more information, contact Dr. Lopez-Berestein at (713) 792-8140, Dr. Newman at (713) 745-3660, or Dr. Madden at (713) 745-3040.

See page 4 for related article.
Pediatric New Agents Working Group Advances the Study of Novel Treatments in Young Patients

by Kate Ó Súilleabháin

A diagnosis of cancer in a child is particularly tragic and often devastating to the family. However, hope does exist for young patients: children tend to respond better to chemotherapeutic agents than do adults, and many of the drugs currently under development appear to be more effective in pediatric cancers than in adult malignancies.

Seeking to improve the outlook for young patients at The University of Texas M. D. Anderson Cancer Center is the Pediatric New Agents Working Group. Established in 1995, the group develops new anticancer therapies for patients younger than 18 years, who usually have less access to clinical trials than adults do. One reason for this difference is that many of the cancers that occur in pediatric patients are rare and biologically distinct from adult cancers. Thus, recruiting young patients in numbers sufficient for a trial can be challenging. “It depends on our referral base and the type of cancer,” said John Kuttesch, M.D., Ph.D., the group’s director and an associate professor in the Division of Pediatrics. “Patients are referred by outside oncologists, through inquiries of families and patients, and through information available on the [Division of] Pediatrics Web site or in publications such as OncoLog,” he said.

Another reason children may have less opportunity for inclusion in clinical trials is that researchers have traditionally tested drugs in adults before using them in children. However, the results of testing a drug exclusively in adults may be misleading. “One problem with evaluating new drugs only in adults is that lack of efficacy might lead to abandonment of the drug,” said Cynthia Herzog, M.D., a member of the group and an associate professor in the Division of Pediatrics. “So even though it might be very effective in pediatric patients, you never get a chance to test it [in children],” she said.

What may be changing. According to Dr. Kuttesch, the U.S. Food and Drug Administration recently implemented a policy designed to encourage the development of new agents for use in children and adolescents. “Whoever submits a plan to test a new agent in pediatric patients gains six months to one year of marketing and manufacturing exclusivity. This means the drug owner has exclusive control of the agent for up to a year to evaluate that drug in children,” he said.

While the Pharmaceutical Development Center at M. D. Anderson facilitates both preclinical and clinical testing of new agents, the Pediatric New Agents Working Group focuses on clinical development. (An exception is a study of liposomal interleukin-12 in a mouse model that is being led by Laura Worth, M.D., Ph.D., an assistant professor in the Division of Pediatrics, and Eugenie Kleinerman, M.D., professor and chair of the Division of Pediatrics. This preclinical study is being performed to obtain data sufficient to warrant study of this immune stimulant in pediatric patients.)

Drugs currently under development target a diverse array of pediatric cancers, and most of the patients enrolled in the trials have recurrent malignancies or disease refractory to standard therapy. “Ideally, we select drugs for testing based on whether we think they will show some benefit in a particular [pediatric] cancer. Our selection of drugs for clinical trials is based on results of previous lab testing, in vitro results in cell cultures, and previous testing in adults,” Dr. Kuttesch said. He is currently testing liposomal vincristine, a drug that was first studied in adults at M. D. Anderson, for the treatment of relapsed Ewing’s sarcoma and other solid tumors in children. Another drug, clofarabine, is being tested in children with leukemia who are enrolled in a phase I study.

Clinical trials involving pediatric patients also raise important ethical issues. Dr. Kuttesch relies on three criteria for including young patients in clinical trials. “First, there must be a rationale for testing a given drug in a certain type of malignancy,” he said. “The drug must show a mechanism of action specific for that given tumor.” Second, the pharmacologic data must show margins of safety for patient protection. Third, because a child cannot provide consent, the parents or guardians must do so. “Surrogate [informed] consent requires comprehension by the family about what we know and don’t know about a drug,” said Dr. Kuttesch.

Physicians and families interested in clinical trials of agents for patients with pediatric cancers at M. D. Anderson can contact the Pediatric New Agents Working Group at (713) 792-6620.

Dr. Cynthia Herzog, an associate professor in the Division of Pediatrics and member of the Pediatric New Agents Working Group, examines [name redacted].

4 / OncoLog
As Population of Cancer Survivors Grows, Studies of Long-Term Health Effects Become More Critical, Researchers Say

by Dawn Chalaire

As treatments improve, more and more patients are battling cancer—and winning. According to the National Cancer Institute, 8.4 million Americans are living with a history of cancer. But what is cause for celebration is also a source of concern for forward-thinking researchers because very little is known about the overall health of these long-term survivors.

Most of the more serious long-term effects of cancer and cancer treatments are well documented: the surgical defects caused by the removal of a tumor, for example, or the late effects of radiation therapy to certain areas of the body. But what about less serious, chronic conditions that could be caused or aggravated by past cancer therapies?

"There is no documentation of what people who were treated 10 years ago look like—virtually nothing about their medical health," said Rena Sellin, M.D., a professor in the Department of Endocrine Neoplasia and Hormonal Disorders and director of the Life After Cancer Care clinic at The University of Texas M. D. Anderson Cancer Center.

While a good deal of information exists about survivors of childhood cancers, studies of adult cancer survivors have tended to focus only on quality of life and social adjustment. The few studies of survivors of adult cancers that do address medical questions are of discrete groups of cancer survivors or types of disease rather than the population as a whole.

According to Dr. Sellin, this paucity of information was the primary motivation for a survey of adult cancer survivors she began in 2000, along with Pam Schultz, Ph.D., program director for the Department of Endocrine Neoplasia and Hormonal Disorders.

"Usually, research involved in cancer means a better treatment, a new discovery, a better way of doing something to make the patient's outcome better, and we don't think beyond that," Dr. Schultz said. "I think this opens up the idea of a way of looking at patients differently. Once you have cancer, you may never have cancer again, but you must live with the consequences of having had it."

The five-page survey was mailed to 9,512 cancer survivors identified in the M. D. Anderson database in September 2000 as having completed cancer treatment at M. D. Anderson (Continued on page 6)
at least five years earlier. The survey, Dr. Sellin said, was similar to a new-patient history in that it was designed to systematically collect information such as age, sex, important medical diagnoses, past medical history, and social history (e.g., marital status, employment status, and level of education).

“We tried to make it as general, descriptive, and noncommittal as possible,” Dr. Sellin said, adding that they wanted to avoid asking leading questions that might influence the responses. “This is a way to begin gathering some basic descriptive information to see where we should focus.”

According to Dr. Schultz, the researchers hoped to get a total of about 1,000 responses, but three months later, more than 4,000 cancer survivors had already mailed back the survey. This extremely high response rate came as a surprise, as did the respondents’ candor and willingness to divulge additional information about their lives.

“That’s probably going to be one of the richer things we get out of this—what they told us,” said Dr. Schultz. “Some of them would write long letters attached to the survey. They would write in the margins.”

Dr. Schultz took down a huge threering binder—one of several occupying a bookcase in her office—and pointed to comments written in the margins and at the top and bottom of the survey form. “We’re in the process of trying to figure out a way to capture all of these extra comments,” she said.

Drs. Sellin and Schultz have completed their preliminary analysis of data from the survey and are weighing the next step in their investigation. In a presentation at the 38th annual meeting of the American Society of Clinical Oncology in May, they reported that only about 34% of the cancer survivors responding to the survey indicated having significant health problems since their cancer treatment ended.

“So they’re really doing quite well,” said Dr. Schultz, “and I think that’s one of the things that we can glean from this: What did we do right? Instead of looking at the patients who failed, to see what happened to them.”

Preliminary analysis of the data indicates, however, that cancer survivors younger than 45 years had arthritis, hearing impairments, and heart disease more frequently than did people of similar age in the general population. One possible explanation is that some cancer therapies can speed up the aging process.

“Maybe the issues are not different,” Dr. Sellin said, “but the timing is different.”

The only way to find out for sure which, if any, of the health problems reported by cancer survivors are the result of their having had cancer, said Dr. Sellin, is to compile a national database of cancer survivors, similar to the Surveillance, Epidemiology, and End Results (SEER) Program database, and systematically analyze the data.

The next step would be to decide what areas (e.g., type of cancer, treatment, or age) to focus on in future studies. “We need to look descriptively at all of the information that we have. We haven’t even begun to scratch the surface,” Dr. Sellin said. “Gradually, we will carve out the different diseases, treatments, and other factors that might be influencing the health profile. In a few years, we will take that and try to dig one layer deeper. The specialists in these different areas will have to be very directly involved in designing the kinds of trials and deciding what questions should be asked and how information should be interpreted.”

Research into the long-term effects of cancer and its treatments could also affect treatment decisions in some types of cancer.

“If you were to have a disease for which two treatments were equally effective, and you could know that one of them had more serious late effects than the other, then you would be in a position to select the effective combination of treatments that is less toxic down the road. So you need a health profile of ‘down the road,’” said Dr. Sellin. “If we could understand efficacy equivalency and delayed health profiles better, we could begin to look at both and make a recommendation.”

Most of the current guidelines for cancer care do not extend beyond five years past the completion of treatment. Once these studies of cancer survivors are completed, the information could be compiled (as in a textbook) and used to guide the care of cancer survivors. One possible model, Dr. Sellin said, is that patients who have been successfully treated for cancer would return periodically for the rest of their lives to a cancer center or related facility to have their medical history updated in the context of their background and to take advantage of any new information that had become available since their last evaluation. Any recommendations made during their visit could be documented for them to take back to their primary care physician.

For more information, contact Dr. Sellin at (713) 792-2841 or Dr. Schultz at (713) 792-2840.
Taking a More Active Role in Your Own Health Care

In the doctor's examination room, we've all felt a bit like the Cowardly Lion confronting the "Great and Powerful" Wizard of Oz, afraid to speak up lest we anger our potential benefactor. Fear is not the only thing that keeps us from getting the most out of our interactions with doctors, however. Shyness, depression, or not wanting to appear ignorant keeps many patients from expressing their thoughts. Regardless of the reasons, withholding information—for example, not telling the doctor about chronic or recurrent pain—or failing to ask questions could contribute to a patient’s receiving less than optimal care.

According to Marlene Z. Cohen, R.N., Ph.D., director of Applied Nursing Research at M. D. Anderson Cancer Center, the most important question a patient can ask is "What do I need to know?" If the first, second, or third reply does not thoroughly answer the question, keep asking until you fully understand your treatment and condition. Equally important, Dr. Cohen added, is the hospital staff's responsibility to inform patients about their treatment. "It is our responsibility as professionals to let them know what they need to know," she said. However, patients should not rely on this ideal.

As a patient, you can make the most of your doctor visits by applying one or more of the following tips.

**#1.** Before you visit the doctor, make a list of questions and concerns. The following questions can help you construct your own list to take with you to the doctor:

- **Questions to Ask My Doctor**
  - **What is wrong with me?**
  - **What are my treatment options?**
  - **What medications will I have to take, and what will be their side effects?**
  - **What are the risks of these treatments and medications?**
  - **How will I feel during treatment?**
  - **How long should I expect to be in the hospital?**
  - **Will I be able to continue working or caring for my family?**
  - **Will I be physically or mentally impaired?**
  - **What else do I need to know?**

Do not limit the concerns you express to only those things you think are relevant. Express all of your concerns openly and honestly; any bit of information may be helpful. For example, that pain in your knee you think is unimportant may help your doctor make the correct diagnosis and give you the proper treatment. According to Dr. Cohen, patients often do not report discomfort or pain because they do not want to distract the doctor from treating the primary disease or because they think the pain is not treatable. But in fact, most of the time pain can be treated, and managing pain can improve the outcome of a patient's primary treatment.

**#2.** Doctors and other clinicians are always on a tight schedule and are concentrating on what they think you should know. Therefore, trying to ask questions while the doctor is giving you important information is a real challenge. Do not let the doctor cause you to lose your train of thought or make you feel that you shouldn't ask questions. Do, however, let the doctor tell you what he or she thinks you need to know. Otherwise, you could have all of your questions answered and still miss important information about your care.

**#3.** No one feels totally at ease in a hospital, and that makes concentrating and remembering the things you want to say difficult. Bring a friend or family member with you to the hospital, not only to make you more comfortable but also to help you remember what the doctor said and remind you of your questions and concerns. You could also (with your doctor's permission) bring a tape recorder with you when you visit the doctor. That way, you can record the conversation and listen to it as often as you need to, until you understand everything the doctor said.

Above all, participate in your own health care. By being more assertive, you can help your doctor provide you with the best treatment possible.

To learn more, see Speak Up™ for Healthcare Safety on the M. D. Anderson Web site at <www.mdanderson.org/patients_public/current_patients/> or visit the American Cancer Society and the National Cancer Institute Web sites for information about prevention, treatment, medication, patient services, research, and more (<www.cancer.org> and <www.nci.nih.gov>, respectively).

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

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

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Patients and Physicians: Partners in Health Care

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“...We need to encourage our patients to take a more active role and invite them to join us in a dialogue about their health-care needs.”

The mission of all clinical practices is to operate in an efficient, profitable manner, to deliver the highest quality of patient care, and to achieve patient satisfaction. To accomplish these goals, we must forge patient-physician partnerships that are built on communication and understanding—partnerships built on trust.

Unfortunately, we are pressured by our workloads and by economic issues to function in a manner that uses our time most efficiently. To bill appropriately and legally, we are expected to accomplish more and more during a patient encounter.

Because we have been trained to arrive at a differential diagnosis and treatment plan, it is in the patient’s best interest for the clinician to direct the patient-history interview. But if we, from the beginning of the medical encounter, give the patient a measure of control by encouraging him or her to contribute information, ask questions as they occur, discuss concerns, and participate in treatment decisions, a partnership is forged.

Trust is established when we gain the patient’s permission and proceed in a sensitive and attentive manner, allowing the patient to offer information rather than extracting it. We should also encourage patients to bring a family member or friend with them for comfort and support. Often, the patient, under the stress of the encounter and illness, may not ask questions or express concerns, while those accompanying the patient may think more clearly and remember the discussion and instructions better.

The lack of control that patients have over health-care decisions has been identified as one of the principal forces behind the explosion of complementary and alternative medicine during the past decade. The authoritarian model is being discarded by our culture and our courts and replaced by a model that gives patients autonomy. But we need to encourage our patients to take a more active role and invite them to join us in a dialogue about their health-care needs. This may require us to become more comfortable with their knowledge and questions.

If we support our patients in making informed, safe, and appropriate medical choices, we will accomplish the goal of the patient-physician partnership.
CLINICAL PRACTICE GUIDELINES
Quarterly Supplement to Oncolog
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About These Clinical Practice Guidelines

These guidelines may assist in the diagnostic evaluation and treatment 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.mdamderson.org.

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CLINICAL DISCUSSION:
Cervical Cancer

Scope of This Guideline

This discussion represents M. D. Anderson's guidelines for the treatment of identified cervical cancer. Guidelines for the diagnostic evaluation of patients with an abnormal Papnicolaou's cervical exfoliative cytology (Pap) test result or a pelvic mass will appear in the next two issues of Compass. All of these guidelines are available on the Internet via M. D. Anderson's Home Page.

The recommendations cited here are, where possible, based on data from clinical trials, and where such data do not exist or are not conclusive, they reflect a consensus of expert opinion.

Synopsis & Highlights

Overview

Cervical cancer is the most common gynecologic cancer worldwide, but where widespread screening using the Pap test and pelvic examination is available, both the incidence of and the mortality rate associated with this disease have dramatically decreased, as early identification of cervical dysplasia and microinvasive disease has led to early treatment and better outcomes for women with these lesions. Screening by pelvic examination and Pap test should be done yearly, starting at age 18 or at the onset of sexual activity, and should continue throughout a woman's life.

Risk factors for cervical cancer include first intercourse at an early age, multiple sexual partners, and unprotected sexual intercourse. Human papillomavirus (HPV) is a very important factor, particularly subtypes 16, 18, 33, and 35, which have been associated with invasive lesions. Smoking and immunosuppression are additional risk factors. Ninety percent of cervical carcinomas occur in the transformation zone of the cervix, and most are squamous cell carcinomas. However, says Dr. Ramirez, "There has been a recent shift in the incidence and pattern of histologic subtypes, and we are now seeing an increased incidence of adenocarcinomas."

Cervical cancer spreads metastatically by direct extension to contiguous tissues, organs, and other structures and also via the lymphatic system (most commonly, this occurs sequentially to paracervical, parametrial, pelvic, common iliac,

(Continued on next page)
para-aortic, and supraclavicular nodes). Hematogenous metastasis to distant sites (most commonly the lungs or bone) is seen in advanced disease. "Fortunately," says Dr. Effiel, "most patients with cervical cancer present without distant metastases, even in cases of locally advanced disease, so many can be cured with local treatment." Recurrent disease is, however, complex and difficult to treat, so it is important to provide the most thorough and specific treatment up front, she says.

Small (< 4 cm), localized cervical cancers are most often treated surgically unless there are surgical contraindications, in which cases radiotherapy (XRT) may be used as effectively. Once disease spreads beyond the cervix, XRT and chemotherapy, usually delivered concurrently, become the primary treatments. As the treatment of cervical cancer may include surgery, chemotherapy, and XRT, referral to a gynecologic oncologist who is in a position to coordinate multidisciplinary treatment is recommended.

Initial Evaluation & Staging
Cervical cancers are staged pathologically and clinically (rather than surgically) and classified according to the staging system recommended by the Federation Internationale de Gynecologie et d'Obstetrique (FIGO). Early-stage cancers are classified histologically according to the degree of lesion invasion into the stroma of the cervix. For more advanced cancers, the stage is based on the extent of disease beyond the cervix, as revealed by pelvic examination, chest x-ray, and imaging studies of the pelvis. For pelvic imaging, Dr. Levenback says, "We now rely on magnetic resonance imaging (MRI), which is very accurate in screening patients for bladder and rectal involvement. We perform cystoscopy and sigmoidoscopy only if there are signs of involvement on the MRI scan or upon clinical examination."

Dr. Levenback recommends that the MRI study include the kidneys and pelvis (i.e., from the para-aortic nodes to the renal vessels). Where MRI is not available, computed tomography scanning or intravenous pyelography and barium enema may be used to ascertain the extent of pelvic disease.

If a visible lesion is discovered during a clinical examination, the physician should forgo the Pap test and proceed directly to biopsy. Dr. Levenback recommends a punch biopsy rather than a cone biopsy in this situation because the accepted practice is to refrain from performing a radical hysterectomy for 4 to 6 weeks following a cone biopsy; thus, a cone biopsy may cause an unnecessary delay in treatment.

Primary Treatment

Microinvasive Disease (Stage IA1)
For nonvisible lesions discovered as the result of an abnormal Pap test, Dr. Ramirez recommends an immediate cone biopsy with endocervical curettage. This procedure entails the removal of the transformation zone of the uterine cervix. When biopsy sample margins are negative, the physician might elect to defer hysterectomy and provide close surveillance, including pelvic examination and Pap test every 3 months for at least 2 years. According to Dr. Ramirez, this may be a reasonable course of action in patients with squamous cell carcinoma even when biopsy sample margins are positive (although such patients are considered to be at higher risk), assuming that close surveillance is provided. Further, he cites new studies that show that a simple hysterectomy is adequate at the microinvasive stage for both squamous cell carcinomas and adenocarcinomas. Previous recommendations for microinvasive adenocarcinoma included radical hysterectomy and did not allow for the preservation of fertility.

Invasive Disease
Patients whose biopsy samples reveal > 3 mm of stromal invasion (stages IA2-IB1) are treated with either radical hysterectomy or XRT. Radical hysterectomy consists of removal of the cervix, uterus, parametrial tissues, and upper fourth of the vagina and includes dissection of the pelvic and para-aortic lymph nodes. It does not routinely include removal of the ovaries. Where there is a choice between surgery and XRT in the guideline, the two treatments have the same statistical effectiveness; however, radical hysterectomy should be reserved for patients whose volume of disease is small and likely to be completely removed by the surgery. Otherwise, adjuvant XRT will still be necessary, and patients experience more morbidity from the two procedures combined than with XRT alone. XRT also is favored in cases of adenocarcinoma with a histologic grade of 2 or 3, where there is lymphatic or vascular invasion, or where surgery may be less well tolerated. Where the choice still seems
Cervical Cancer (2)

SALVAGE THERAPY FOR RECURRENT CANCER

Pelvic recurrence

Prior XRT?

Recurrence in central pelvis

Metastasis to other sites

Stage* IVC or extrapelvic recurrence

Treatment

SURVEILLANCE

Individualize palliative care and surveillance as appropriate

XRT with possible curative intent or
Consider chemoradiation

Consider total pelvic exenteration or
Clinical trial or
Cisplatin (depending on renal function)

Clinical trial or
Cisplatin (depending on renal function)
or
Carboplatin (AUC 5-7) or
Supportive care or
Consider resection for isolated disease recurrence

Consider palliative XRT or chemoradiation or
Clinical trial or
Consider resection in selected patients or
Cisplatin (depending on renal function) or
Carboplatin (AUC 5-7)

XRT annually
Year 1: physical exam with pelvic every 3 mo, CXR every 6 mo, Pap annually
Years 2-5: physical exam with pelvic every 6 mo, CXR with every 6 mo, Pap annually

*Disease is staged according to the system of the Federation Internationale de Gynecologie et d'Obstetrique (FIGO).
**Relative indications in favor of XRT rather than radical hysterectomy: adenocarcinoma grade 2 or 3 and 4 cm of lymphatic or vascular invasion, weight > 60 kg, advanced age, or comorbid conditions.
***Acute pathologic factors include positive nodes, margins, or parametrium; deep invasion; lymphatic or vascular space invasion; or tumor > 4 cm.
****Chemoradiation is recommended for patients with positive nodes, margins, or parametrium. Pelvic XRT should be considered for patients with deep invasion, lymphatic or vascular space invasion, or tumor > 4 cm.

This practice guideline was created by the National Comprehensive Cancer Center Network and was modified by the faculty of the Department of Gynecologic Oncology at The University of Texas M. D. Anderson Cancer Center for our own patient population.

(Continued on next page)
locoregionally advanced disease. At M. D. Anderson, platinum-based chemotherapy is usually given concurrently with XRT in these cases.

**Surveillance**

After treatment is completed, patients usually return one month later for a pelvic examination. A Pap test is not usually done until 4 months following completion of XRT. Follow-up visits are scheduled every 3 months during the first year, every 4 months during the second year, and every 6 months for the next 3 years. Other recommended screening tests are shown in the guideline.

**Recurrence**

Treatment of recurrent cervical cancer depends upon the location of recurrence (pelvic or extrapelvic) and upon prior treatment. Chemoradiation is considered first for patients who have not had prior XRT and may also be an option for those with recurrent disease in sites not previously irradiated. Surgery or chemotherapy is recommended for patients with recurrent disease in sites that were previously irradiated. Surgically, total pelvic exenteration includes the removal of the cervix, vagina, uterus, bladder, rectum, and rectal sigmoid and the subsequent creation of bladder and colostomy conduits. Modifications of this procedure to include removal of only the anterior or posterior structures may be possible in some patients, sparing the need for colostomy or urinary diversion. Creation of a neovagina using the myocutaneous flap from the patient's inner thigh is an option to consider for patients who are sexually active. Pelvic exenteration should be considered only in cases where disease appears to be confined to the central pelvis, increasing the likelihood that this procedure will remove all residual disease. Where there is extrapelvic disease, further surgery should be limited to resection of isolated lesions, with chemotherapy as the primary treatment option.

**Authors’ Perspectives**

At least 50% of cervical cancers in the United States occur in women who have not had a Pap test in 5 or more years. Underscoring the importance of annual screening, all of our experts agree that this is the single most important message about cervical cancer and urge physicians to encourage their patients to get annual screening examinations. According to Dr. Eifel, older and postmenopausal women are of particular concern, as many of them stop having gynecological exams and Pap tests as they advance beyond their reproductive years. According to Dr. Levenback, “Even in this high-tech era, a woman’s best protection against dying of cervical cancer is the annual Pap smear.”

The radiological and surgical procedures used to treat cervical cancer are specialized and unique to the treatment of this disease. Radical hysterectomy, for example, is a surgical procedure that is rarely used for the treatment of any other condition, and the radiotherapy techniques are completely specialized to this disease. This, combined with the fact that invasive cervical cancer is somewhat uncommon, means that many treatment centers do not have extensive day-to-day experience with this disease. Dr. Eifel cites a recent survey showing that 80% to 85% of non-academic XRT facilities treat fewer than 3 cases of cervical cancer per year. “What this means,” she says, “is that for this particular cancer, it is most desirable to seek care in a setting where there is experience with such techniques and also where multidisciplinary care can be coordinated. It is important, for example, that the pathologists and surgeons be accustomed to analyzing and handling specimens taken from previously irradiated tissues.”

**References & Suggested Reading**


National Cancer Institute Clinical Announcement: Concurrent chemoradiation for cervical cancer. Bethesda, Maryland, National Cancer Institute, February 1999


