Non-Hodgkin’s Lymphoma
Therapy Innovations Improve Patient Response

by Don Norwood

Building on a drug regimen developed 25 years ago at The University of Texas M. D. Anderson Cancer Center, physicians are crafting therapies producing longer relapse-free survival in patients with non-Hodgkin’s lymphoma (NHL), even in those whose prospects are dimmed by poor prognostic variables. Largely responsible for the advances are innovations by faculty and molecular tests that have raised the bar in evaluating response, challenging researchers to produce more effective interventions.

For about the past 25 years, the standard treatment of NHL has been a chemotherapy regimen developed at M. D. Anderson—cyclophosphamide, doxorubicin, Oncovin (vincristine), and prednisone (CHOP) alone or in combination with radiation therapy—according to Fernando Cabanillas, M.D., professor of medicine in M. D. Anderson’s Department of Lymphoma/Myeloma. About 50%–65% of NHL patients have a complete response to CHOP, he said, but experience with those whose disease did not respond well to the CHOP regimen led physicians at M. D. Anderson to modify the regimen and to develop new ones.

One particularly troublesome type of NHL is mantle cell lymphoma, a rare disease found mainly in people over age 50 that shares features of both indolent and aggressive lymphomas. It accounts for about 2%-10% of all NHL. Altogether, indolent (slow-growing) lymphomas make up 40% of all NHL, and the remainder are aggressive.

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Mantle cell lymphoma, according to Dr. Cabanillas, is regarded as the lymphoma least responsive to any treatment. However, a chemotherapy regimen typically used against acute lymphoblastic leukemia (ALL) called hyperCVD (twice-daily cyclophosphamide, vincristine, Adriamycin [doxorubicin], and dexamethasone) that was adapted for mantle cell lymphoma by Dr. Cabanillas and Issa Khouri, M.D., assistant professor of medicine in the Department of Blood and Marrow Transplantation, is changing that.

"The results over the past three years have really been much better than we expected," said Dr. Cabanillas. He said that researchers had used the traditional CHOP regimen against mantle cell lymphoma but that most agree it didn't really work very well. The complete response rate was low and the median survival was about three years.

"We divide patients into two categories: those who are younger than 65, in which case they will be eligible for a bone marrow transplant following programs of hyperCVD plus methotrexate and cytarabine, and those over 65, who will only get the straight hyperCVD and methotrexate-cytarabine programs but no transplant," Dr. Cabanillas said.

The hyperCVD regimen was first brought to M. D. Anderson by Hagop Kantarjian, M.D., professor of medicine in the Department of Leukemia, who adapted it for adult ALL from a pediatric ALL protocol. Cabanillas said that after the success of hyperCVD against ALL, the regimen was tried by Maria Alma Rodriguez, M.D., for mantle cell lymphoma "out of desperation" because the disease was so hard to treat. Dr. Rodriguez is an associate

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Non-Hodgkin's Lymphoma Protocols Feature Chemotherapy, Radiotherapy, and Monoclonal Antibodies

Clinical studies for treatment of non-Hodgkin's lymphoma currently under way at The University of Texas M. D. Anderson Cancer Center include the following. Contact the M. D. Anderson Information Line or visit the M. D. Anderson clinical trials site on the World Wide Web (see numbers and addresses below) for more information.

- Phase II trial of high dose methotrexate/ara-C and HCVAD for relapsed/refractory mantle cell lymphoma and their blastic variants (DM97-201). Physician: Jorge Romaguera, M.D.
  To be eligible for this study, patients must have a confirmed diagnosis of nodular or diffuse mantle cell lymphoma or a blastic variant. They may have previously received treatment with the drugs used in this protocol, but not according to its doses and schedule. Patients must be 16 years or older and have a performance status of ≤2. Required blood counts are as follows: bilirubin, <1.5 mg/dL; serum creatinine, <1.5 mg/dL; unless involved by lymphoma; absolute neutrophil count (ANC), >1000/mm³; and platelets, >100,000/mm³, unless involved by lymphoma. Cardiac ejection fraction must be ≥50%. Exclusion criteria include concurrent or previous malignancy with poor prognosis.

- Intensive therapy for mantle cell lymphoma (DM94-130). Physician: Issa Khouri, M.D.
  In this study, described in the columns above, patients must have a confirmed diagnosis of poor-risk mantle cell lymphoma (diffuse, nodular, blast) or chronic lymphocytic leukemia (CLL) with t(11;14) and have a performance status of ≤2. They can be previously untreated or at any relapse. Required blood counts are as follows: bilirubin, <1.5 mg/dL; serum creatinine, <2.0 mg/dL (<1.6 mg/dL if candidate for bone marrow transplantation), unless kidneys were involved by lymphoma; ANC, >1000/mm³; and platelets, >100,000/mm³, unless attributable to extensive bone marrow involvement. The patient must be a bone marrow transplantation (BMT) candidate. There must be no CNS
professor of medicine in the Department of Lymphoma/Myeloma. “ALL and mantle cell lymphoma aren’t really similar disorders, but since we had tried so many things in mantle cell lymphoma and nothing really worked, we decided to give a try to something different, and we had some responses,” Dr. Cabanillas said. “So then we started looking at it systematically, and it’s worked out much better than anything we’ve used in the past.”

The hyperCVAD regimen actually involves two regimens. The hyperCVAD combination is alternated with high doses of methotrexate and cytarabine for four courses. Then high-dose cyclophosphamide and total-body irradiation are followed by autologous stem cell transplantation.

The early results of a study of hyperCVAD for mantle cell lymphoma explain Dr. Cabanillas’ praise. According to Dr. Khouri, about 75% of the mantle cell lymphoma patients who have received hyperCVAD are alive in remission three years after treatment. In comparison, about 20% of comparable patients who received CHOP for mantle cell lymphoma were alive in remission after three years.

“It is a major step forward,” Dr. Khouri said.

In addition, Dr. Khouri said that 92% of the patients with mantle cell lymphoma who received hyperCVAD have had signs of tumor volume reduction, a result that is helping garner attention for the regimen.

“We were hoping we could improve the percentage of patients alive in remission by 25%,” Dr. Khouri said. “We were surprised to see such a dramatic improvement.”

Significant strides have also been made in the treatment of relapsed indolent lymphomas. Peter McLaughlin, associate professor of medicine in M. D. Anderson’s Department of Lymphoma/Myeloma, has developed a combination of the drugs fludarabine, mitoxantrone (Novantrone), and dexamethasone (FND) that has produced molecular responses in salvage therapy for these lymphomas. Researchers use the polymerase chain reaction test to detect bcl2 rearranged cells in bone marrow as an indication of residual disease. They found such measures of molecular response correlate better with outcome than clinical assessment measures or prognostic variables.

“Molecular responses are not easy to come by using standard therapy,” Dr. Cabanillas said. “But with the FND regimen, we were able to get a relatively high molecular response rate. What we observe is that it’s as good as a more intensive ATT (alternating triple therapy) regimen in inducing molecular responses.”

Dr. Cabanillas said the next step for the FND regimen is to develop it as the frontline therapeutic approach for stage IV indolent lymphomas.

“We’re now doing a study that is very exciting because there is a new drug on the market called Rituxan, which is a monoclonal antibody able to identify the CD20 antigen, which is expressed in the vast majority of B-cell lymphomas,” Dr. Cabanillas said.

M. D. Anderson participated in the multi-institutional study that led to the approval of that drug. “We put more patients in the study than any other institution,” said Dr. Cabanillas, “so we have a lot of experience with that agent. We decided we would do a study, which we just initiated, in which we’re using FND in combination with Rituxan based on the fact that Rituxan has a 50% response rate as a single agent in relapsed lymphomas.”

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involvement and no comorbidity that preclude intensive chemotherapy. Prospective patients must not have received extensive prior radiotherapy.

• A study of 131 I-LYM-1 at a dose of 60 mCi/m2 in the treatment of refractory B-cell non-Hodgkin’s lymphoma (ID94-015). Physician: Peter W. McLaughlin, M.D.

Patients with B-cell non-Hodgkin’s lymphoma of intermediate or high-grade histology whose disease has proved refractory to intensive multidrug chemotherapy are eligible for this study. Also eligible are patients who have received common frontline multidrug chemotherapy that failed to produce a response or produced a response followed by relapse. Patients must be ≥18 years of age and have a life expectancy of at least three months and a performance status ≥0 at initial treatment with this protocol. Disease must be measurable and may include tumors in the liver and/or bone. Ineligible are most patients with a second primary malignant neoplasm (including chronic lymphocytic leukemia), lymphomatous meningitis, or other central nervous involvement with leukemia.

• Fludarabine, mitoxantrone, and dexamethasone (FND) plus chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) for stage IV indolent lymphoma (DM97-261). Physician: Peter W. McLaughlin, M.D.

Previously untreated patients who are <76 years old and have stage IV follicular lymphoma or small cell lymphocytic lymphoma are eligible for this trial. This includes patients with follicular large cleaved cell lymphoma. Patients will undergo treatment with fludarabine, mitoxantrone (Novantrone), and dexamethasone combined with IDEC-C2B8 (Rituxan). Ineligible are patients in whom histological grades differ site to site and those in whom prognosis is poor because of an antecedent malignancy. Other exclusion criteria include the following: an absolute peripheral granulocyte count of <1,000/mm3 and a platelet count of <100,000/mm3 (unless the altered values are caused by marrow infiltration by lymphoma or hypersplenism); a bilirubin value >1.5 mg/DL and a serum creatinine level >1.5 mg/dL (unless values are irregular because of lymphoma).

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phoma, which puts it in a category of very active drugs with very good duration, very minimal toxicity, and no overlapping toxicity with chemotherapy,” Dr. Cabanillas said.

In seeking a better molecular response in the treatment of advanced indolent lymphomas, Cabanillas said that researchers are seeking to eliminate every possible sign of minimal residual disease, which means looking in both blood and bone marrow for response.

“We have two areas that we look at because, in some areas, patients might attain a molecular response in the blood but not in the bone marrow, or vice versa. It’s a complicated thing. You look at blood only, for example, it’s still better than looking at the clinical response. But it’s probably going to be even better if you can get a molecular response both in the blood and the marrow,” Dr. Cabanillas said.

Like advanced indolent lymphomas, early stage follicular lymphomas often do not have a positive molecular response to standard chemotherapy. Early stage follicular lymphomas account for 20%-25% of all NHL, so this lack of response is particularly troublesome. To meet the challenge in this area, Dr. Cabanillas and James Cox, M.D., professor of radiation oncology and head of the Division of Radiation Oncology, are making inroads by comparing very extensive radiation therapy with the high-dose ATT chemotherapy regimen.

A complex regimen, ATT combines the following: CHOP-bleo (cyclophosphamide, doxorubicin, vincristine, and prednisone-bleo) alternating with ESHAP (etoposide, Solu-medrol [methylprednisolone], ara-C [cytarabine], and platinum) and NOPP (Novantrone, Oncovin, procarbazine, and prednisone). Both ATT and the extensive irradiation, which is called central lymphatic irradiation, Dr. Cox said, have accomplished what standard chemotherapy and radiation therapy could not.

“We’re very impressed that they’re both so effective,” Cox said. “Both of these approaches are more effective than more modest treatment approaches.”

Although the radiation treatment used is extensive, it falls short of total-body irradiation (TBI), a fact that Cox finds encouraging, given the positive molecular responses he has seen. Avoiding TBI is important in order to preserve more intensive therapy for subsequent treatment if it is necessary.

“The long-term results of central lymphatic irradiation,” he said, “have been encouraging.”

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- Systemic vs. local therapy for stage I-III low-grade lymphomas monitored by polymerase chain reaction technique (UM92-102). Physician: Fernando Cabanillas, M.D.

This protocol, described in the columns above, is for previously untreated patients with follicular low-grade lymphoma or small cell lymphocytic lymphoma, irrespective of bcl-2 status. Disease must be clinical stage I-III. Patients must be >76 years old, with no divergent histology (e.g., intermediate grade in one site and low grade in another), no history of chronic obstructive or restrictive lung disease, and no antecedent malignancy with poor prognosis.

- A randomized phase III study of melatonin plus CHOP for patients with large cell lymphoma, tumor score <3 (DM98-009). Physician: Maria Alma Rodriguez, M.D.

Patients with large cell lymphoma (except for T-cell phenotype) who are previously untreated and have a tumor risk score of <3 are eligible. Patients must have adequate marrow reserve (ANC, >1000/mm³; platelets, >100,000/mm³), unless lymphoma is cause of low counts. Serum creatinine and bilirubin must each be <2 mg/dL.

For more information about these clinical trials, physicians or patients should call the M. D. Anderson Information Line. Those in the United States, call (800) 392-1611; those in Houston or outside the United States, call (713) 792-6161. Visit the M. D. Anderson Cancer Center clinical trials Web site at http://www.clinicaltrials.org.
Americans spend $10 to $25 billion annually on unconventional or alternative medicine.

A major U.S. medical journal, the New England Journal of Medicine, estimated from a national survey that in 1990 Americans spent almost as much on unorthodox treatment as they did on total out-of-pocket expenses for hospital care the same year. More than 200 alternative therapies are said to be practiced in the United States.

What is alternative medicine?

Alternative therapies are therapeutic practices not widely available at U.S. hospitals and not taught in most U.S. medical schools. If you have been to a chiropractor, a massage therapist, or an acupuncturist, you have been to an alternative medicine provider. Therapies are called alternative therapies when they are used instead of conventional therapies recommended by a doctor trained in medical school. They may also be used with conventional therapies, either with or without a physician’s knowledge. You may hear these same therapies called complementary therapies when a doctor trained in a medical school recommends or approves their use along with other conventional therapies he or she prescribes.

Who uses alternative medicine?

An estimated 40% of Americans have used these therapies. The person who uses alternative medicine, according to the survey named above, was no more likely to be a man than a woman and no more likely to be uninsured than insured. Alternative therapy users were more likely to be 25 to 49 years of age than they were to be older or younger.

They were also more likely than not to have some college education. Some may want a return to less specialized care—a holistic approach—or be searching for more personalized medical care than they have found within conventional medicine.

How do people use alternative therapies?

Patients who use alternative therapies most often add them to conventional therapy, often without disclosing the practice to their physician. Others turn to unconventional therapies when conventional therapies fail or disappoint them. Some research has shown less than 5% of Americans with a medical problem use alternative medicine alone for treatment. Some patients, for example, combine visualization, imagery—unconventional therapies—with traditional treatment, perhaps to better tolerate a painful intervention or to imagine a positive outcome.

What are the potential risks?

The greatest potential risk in using alternative therapies is that a patient will forgo effective therapy for ineffective therapy or that illness will go undiagnosed and untreated. Consequences could range from the insignificant to the life-threatening. Another risk is that a patient’s alternative therapy could affect the outcome of conventional therapy. Drug interactions, as in conventional medicine, remain a serious concern. Also important is whether the remedy enters the body or not. Considerations are different for such therapies as visualization, relaxation, or massage than they are for regimens requiring megavitamins, acupuncture (in which sterilization is an issue), or unproven drug therapy.

What are some guidelines for evaluating alternative therapies?

1. Before substituting an alternative medicine or adding it to your remedies, talk to your physician. Some substitutions and interactions can be fatal. Neither a medical doctor nor an alternative practitioner wants you to suffer harm. Some therapies, such as visualization, are harmless and are found helpful not only by the ill but also by those who are well.

2. Remember that many over-the-counter alternative remedies remain untested. “Natural” does not mean “safe.”

3. Beware of any unconventional therapy that claims to cure cancer or other serious disease.

4. Determine what scientific groups think of the therapy. Is it one the American Medical Association, the American Heart Association, or the American Cancer Society endorses?

5. Consult licensing boards to identify providers who are working within a framework of professionalism, including licensing certification, or other identification of expertise or training.

Research should in time supply answers about safety and effectiveness. For now, open discussion with a physician should help answer questions about therapy choices.

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 outside the United States.

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Careful Inspection, Early Detection Important in Controlling Oral Cancer

by David Babaian and Beth W. Allen

While recognizing the potential gains from prevention studies under way and the curative ability of surgery, Associate Professor of Head and Neck Surgery Gary L. Clayman, D.D.S., M.D., emphasizes that early detection remains the key to controlling oral cancer.

"Without question, early diagnosis is our greatest tool," Dr. Clayman said in a recent interview. "Dentists and primary care physicians are the greatest health care screening providers for oral cancer. Their recognition of this process is critical." The oral cavity extends from the lips to the soft palate and includes the oral tongue as well as the inside portions of the cheeks and dental arches.

To promote prevention, M. D. Anderson initiated clinical trials that have now progressed into national multi-institutional studies headed by Waun K. Hong, M.D., chairman of the Department of Thoracic and Head and Neck Medical Oncology.

Dr. Clayman, who is deputy chairman of the Department of Head and Neck Surgery, said about one-half of patients with oral cancer have advanced disease at diagnosis, which narrows their probability of living five years or more to less than 50%.

Often symptomatic well before they consult a physician, these patients may postpone seeking treatment, often attributing pain to dental or ear ailments. Dr. Clayman said physicians sometimes fail to suspect referred otalgia. Consultation may even be postponed until such other signs as leukoplakia, a precancerous condition, ulcerations, or a neck mass are visible.

Inspection by an otolaryngologist, who will perform a complete head and neck examination, should yield identification of the cancer and detect other abnormalities along the aerodigestive tract, Dr. Clayman said.

Surgical treatment is often curative for stage I or II disease, according to Dr. Clayman, who stressed how organ and function preservation were foremost considerations in planning treatment. "Frequently surgery can be used in early stage disease as a single and curative approach," he said. Patients can avoid long-term adverse effects of radiation therapy, he said, "and still benefit from good functional and cosmetic outcomes, which have an impact on their quality of life—a major issue." Oral cancer at a late stage can have a long-term effect on appearance and the ability to speak or swallow.

Reserving other interventions, in particular radiation therapy, increases treatment options in case of recurrence, metastasis, or second primary malignancies.

"We certainly believe in Anderson's multidisciplinary approaches to all cancers, but we also believe that if a single modality of treatment can be as effective as multiple modalities, then we prefer to treat with a single modality if it will benefit the patient in both the short and the long term," Dr. Clayman said.

To provide comprehensive care, the M. D. Anderson Head and Neck Center coordinates professionals from many disciplines, including surgeons, medical oncologists, and radiotherapist whose practice is devoted to head and neck cancers; speech pathologists; specialized nurses; and nutrition specialists. "It is really a team approach so that we are all working together rather than in 20 individual directions," Dr. Clayman said. "The M. D. Anderson head and neck oncology program was one of the very first to use the multidisciplinary approach to the cancer patient."

"Because it is a very large referral center for all head and neck cancers, we have a tremendous breadth of experience," he said, adding that the staff's focus also increases the depth of knowledge.

The American Cancer Society estimates that 30,300 new cases of oral cancer will be diagnosed in 1998 in the United States, and men are more than twice as likely to develop oral cancer than are women. Though 80%-85% of patients with oral cancer have a history of tobacco use and most are older than 40 years of age, Dr. Clayman says the incidence of oral cancer appears to be rising in the young and in the aged.

"We're seeing cases in much younger patients. There appears to be an evolution, an increasing

Head and neck surgeon
Gary L. Clayman, D.D.S., M.D., performs a digital examination of thyroid and parotid glands
incidence of oral cancer, in particular in tongue cancer, among young patients, many without significant tobacco histories,” he said. “As the U.S. population continues to age, we’re also getting the other end of the spectrum.”

Though deaths from oral cancer have been decreasing, Dr. Clayman said claiming “significant strides” would be unwise because changes are not owed to dramatic improvements in treatment and decreases are not as great as specialists would like to see.

Because patients who have had oral cancer are at higher risk of developing other cancers, Dr. Clayman said, “We do ask these patients to consider prevention strategies. I’m always very cautious,” he said. If a patient is in the fourth to sixth decades of life, he proposes lifelong annual screening.

“For female patients: When was their last mammogram? When was their last Pap smear? For male patients: Have they had a prostate exam? For men or women: Have they had a colonoscopy or at least an evaluation? When was their last chest x-ray? I think those are very important issues because the greatest risk of cancer is having a prior cancer,” he said.

“It is not infrequent that we see patients who may be referred for a malignancy or even a suspected malignancy, but they haven’t been evaluated for other cancers or precancerous entities that may occur,” Dr. Clayman continued, “so you can make these evaluations a health care opportunity.”

To continue to offer new treatment strategies to patients and to increase understanding of oral cancer, Dr. Clayman said a tremendous amount of research is being done. Apart from Dr. Hong’s work, approaches also include gene transfer and virus replication studies, slow-release chemotherapies, and antiangiogenesis research.

FOR MORE INFORMATION, please contact Dr. Clayman at (713) 792-8837 or call the M. D. Anderson Information Line at (800) 392-1611 or (713) 792-6161.

“Is Today the Day I Find a Lump?”

Tamoxifen Helps Women Escape Breast Cancer’s Shadow

by Alison Ruffin

You would never know it from looking at her, but she has lived in a shadow.

Growing up in the tradition of Houston horsemanship, was reared in a family of equestrians and has worked for the Houston Livestock Show and Rodeo since 1977. T

radiates a robust energy and positive manner, belying the fear that has become her companion in life.

Doctors have told her she has a higher than average risk of breast cancer.

“Is today the day I find a lump?” she says. “This is something I think about every day.”

For this reason participated in a breast cancer prevention trial that began six years ago and was halted recently, 14 months early, because of findings that the study’s drug, tamoxifen, reduced the incidence of breast cancer in high-risk women by 45%.

Realizing tamoxifen’s effectiveness, researchers did not want to withhold it any longer from women who could benefit from it. The drug has been used since the 1970s for breast cancer treatment.

With more than 300 women volunteering, The University of Texas M. D. Anderson Cancer Center had the largest study population in this multisite study funded by the National Cancer Institute. A total of 13,388 healthy women were recruited nationwide at 270 sites.

In the trial, researchers also discovered that women taking tamoxifen had fewer bone fractures of the hip, wrist, and spine than did women in the placebo group).

Although tamoxifen has not been proven to eliminate cancer risk, its ability to reduce risk is an exciting complement to well-documented early detection strategies including mammography, researchers said.

“For women at an increased risk of breast cancer, we now can offer the choice to consider taking tamoxifen to reduce their chances of developing breast cancer,” said Bernard Levin, M.D., vice president for cancer prevention.

In the study, invasive breast cancer developed in 85 women assigned to take tamoxifen but in 154 women assigned to the placebo.

Side effects of tamoxifen included an increased risk of endometrial cancer (33 cases in the tamoxifen group compared with 14 in the placebo group), pulmonary embolism (17 compared with 6), and deep vein thrombosis (30 compared with 19).

The reduced risk encourages

“Now I may not have to worry,” she said, “and that’s very exciting.”

[Image Redacted]
Comprehensive in More Ways Than One

Stephen P. Tomasovic, Ph.D.
Associate Vice President for Educational Programs

M. D. Anderson is designated a comprehensive cancer center by the National Cancer Institute (NCI), but it is comprehensive in ways other than its ability to prevent, diagnose, and treat cancer. It is also comprehensive in its approach to education.

Your patients can access up-to-date cancer information on the Internet or through the public information office here, which besides generating information also provides staff for one of NCI’s regional public information centers. M. D. Anderson’s home page (http://www.mdanderson.org) can provide patients a foothold on understanding cancer, share a perspective on the future of health care from a lecture the Texas-based American Medical Association president-elect gave M. D. Anderson faculty, or teach how to prevent cancer through diet and lifestyle.

Or, maybe you know a science teacher who could benefit from the training programs offered by the Office of Educational Programs. This office monitors, directs, and generates educational enrichment programs for students as well as teachers, including college externs year-round and high school, college, and freshman medical students during the summer.

Medical residents, medical and postdoctoral fellows, and graduate students can also benefit from programs under the M. D. Anderson roof, following a cancer track during their professional training in nationally certified and accredited programs.

For practicing physicians and scientists, the educational opportunities span the spectrum of traditional conferences or lectures to interactive television, Web-based education (NetCME), and telemedicine conferencing. A paperless and confidential interactive system, M. D. Anderson’s NetCME is multilingual: choose from six languages.

Leading these educational endeavors are faculty members who have earned their stripes with both lab coat and stethoscope. Furthermore, M. D. Anderson’s position in the 157-acre Texas Medical Center, which has a ratio of floor space to land area comparable to New York’s Financial District, fosters a synergy that allows faculty to profit from and contribute to broad-based medical and scientific programs with global implications.

Health care professionals who are trained here have every opportunity to learn first-rate methods for achieving first-rate goals.

Yes, these educational opportunities—NetCME, fellowships and clinical rotations, telemedicine conferencing, and others—serve many, but their aim remains singular—excellence. Join us.