Lab to Clinic

Abdul Khokhar is an associate professor of medicine in the Department of Clinical Investigation.

New drug is now entering preliminary trials in humans

Liposomal cisplatin analogue is less toxic and more effective than cisplatin

Since its discovery in 1969, cisplatin has proved to be one of the most effective agents for cancers of the head and neck, bladder, ovaries, and testes, but its use is limited by severe nephro- and neurotoxic side effects. Moreover, tumors eventually develop resistance to it, rendering it ineffective against tumors previously treated with cisplatin. For two decades chemists have been trying to develop new cisplatin analogues that are just as effective as but less toxic than cisplatin. Several analogues that had these qualities have been successfully synthesized, showing good antitumor activity in laboratory studies. Unfortunately, some of these analogues had an additional quality that made prospects for clinical application bleak: the drugs’ lipophilicity made them insoluble in water, thus precluding in vivo administration.

A new family of lipophilic analogues, however, may eventually eliminate these problems. One such member of this family, L-NDDP, is a liposome-encapsulated cisplatin analogue developed by Abdul Khokhar, Ph.D., Department of Clinical Investigation, and Roman Perez-Soler, M.D., Department of Thoracic/Head and Neck Medical Oncology. In animal models, L-NDDP [cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum(II)] was less toxic and more effective than cisplatin, and it showed only minimal cross-resistance with cisplatin. Lack of cross-resistance is a key feature, for it means that cisplatin-resistant tumors may benefit by additional treatment with L-NDDP. A phase I study using intravenous administration in humans has just been completed, and two phase I-II studies using intraarterial and intrapleural administration are now under way.

“L-NDDP is the first antitumor agent synthesized and developed entirely at M. D. Anderson,” said Perez-Soler. “As a result of our efforts, we have been able to make available a new anticancer agent to patients who have failed current therapies. We are proud we could do it within an academic hospital setting, and we feel strongly that we can apply what we learned with L-NDDP to the development of new, innovative therapies for our patients.”

Physician’s proposal sparks chemist’s interest

The story of L-NDDP’s development begins in 1984. By that time, Khokhar had already established himself as an expert in cisplatin analogue synthesis. For 14 years, since his initial work at the University College, London, he had synthesized numerous cisplatin analogues.

“In 1984, my analogue work was progressing nicely. I had just completed a second generation of analogues when Dr. (Gabriel) Lopez-Berestein (Department of Clinical Investigation) approached me with the idea of synthesizing analogues that have a natural affinity for liposomes,” Khokhar said. “The theory was that lipophilic analogues could be more easily entrapped into liposomes and thus more effective. No one had ever done this before. We were the first ones in the world to do it.”

Khokhar had already developed a lipophilic analogue as early as 1982, although he hadn’t intended it for use with liposomes. The analogue was effective and less toxic than cisplatin in laboratory studies, but its lipophilicity made it insoluble in water. It, like other drugs of its kind, had found no clinical application. The possibility of liposome delivery, however, transformed this analogue’s liability into a naturally exploitable opportunity. The incident confirmed Khokhar’s belief that successful drug development depends on having not only resources but also clinical collaborators willing to test and develop the drugs for clinical evaluation.

“One of my goals is to take my science from the bench to the bedside,” Khokhar said, “but without clinicians like Lopez-Berestein and Perez-Soler, I could never do that.”

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Liposomes target specific organs

Liposomes had two endearing qualities: They could, theoretically, allow the infusion of an otherwise uninfusible drug, and they tended to target organs that are rich in phagocytes and that have fenestrated capillaries, such as the liver, spleen, and bone marrow. They could therefore be used to deliver drugs to specific types of tumors. But liposomes also had a quality that was not so endearing: they leaked or dissolved before reaching their intended target.

Attempts at entrapping cisplatin in liposomes had shown a meager 7.4% efficiency, but investigators attributed this more to cisplatin’s lack of lipophilicity. The quality that made cisplatin uninfusible—its affinity for water rather than lipids—is the same quality that made it unsuitable for liposomes. But with a lipophilic analogue, Khokhar was confident that he and his collaborators could improve on 7.4%, although he well suspected that lipophilicity, in itself, would not guarantee efficient encapsulation. Khokhar knew that a lot of work testing various structural modifications lay ahead. The major questions were, would such modifications improve encapsulation efficiency enough to ensure clinical utility, and would these modifications preserve antitumor activity while minimizing toxic effects?

Perez-Soler, who had joined Lopez-Berestein’s laboratory one year before to develop liposome technology for the delivery of chemotherapeutic agents, went to the laboratory with the analogue Khokhar had developed in 1982. “Dr. Perez-Soler did all of the painstaking, difficult experimentation, testing the analogue with various formulations. Without his dedication, our progress would not have been possible,” Khokhar said.

Chance reading of engineering newsletter provides due to L-NDDP

For a first attempt, Perez-Soler’s results were striking: a 50% entrapment efficiency, about six times better than that of cisplatin liposomes. Nevertheless, to maximize encapsulation efficiency, they decided to modify the structure of their current analogue. Their research was helped along by Khokhar’s chance reading of Chemical and Engineering News, in which he noticed an advertisement for neodecanoic acid. The advertisement gave him an idea that would ultimately result in L-NDDP. “Neodecanoic acid is used as a detergent in the oil industry. It has no antitumor activity,” Khokhar said, “but it interested me because of the number of carbons it contains. In general, the more carbons a molecule has, the more lipophilic it is.”

Khokhar decided, therefore, to use neodecanoic acid as a way to add more carbons to a specific part of the analogue molecule. The result was L-NDDP, an analogue that has a chain of 10 carbons attached to the platinum atom. (L-NDDP also differs from cisplatin in that it contains a molecule called diamminocydohexane, a modification that Khokhar had helped discover in the early 1970s. Many of his analogues developed since that time contain this modification, because it confers non-cross-resistance with cisplatin.) L-NDDP had an entrapment efficiency of greater than 95%. In addition, Perez-Soler found that it could be easily prepared as a lyophilized powder that, upon reconstitution on the day of intended use, would produce a suspension of liposomes containing NDDP. When tested in five tumor models, it showed little nephrotoxicity, better antitumor activity than cisplatin, and non-cross-resistance. It did, however, cause myelosuppression.

These encouraging results encouraged Perez-Soler to perform extensive toxicity studies in dogs, the results of which were used to apply for FDA approval to start clinical trials. An investigational new drug exemption was approved in 1989, and a phase I study continued on page 5
Brief counseling could double quit rate

The physician’s role in smoking cessation

About 2.5 percent of American smokers quit smoking each year. However, with more physician intervention, the quit rate could double to 5 percent, said Al Kondo, Ph.D., M.P.H., instructor in cancer prevention at The University of Texas M. D. Anderson Cancer Center. That increase may sound miniscule, Kondo said, but it translates into thousands of additional ex-smokers a year. “We know that 434,000 Americans die of smoking-related causes annually,” he said. “Physicians can do a lot to change this.”

According to the National Center for Health Statistics, smokers visit a physician an average of 4.3 times a year, and 70 percent of all smokers see a physician at least once a year. Thus, physicians have the opportunity to deliver a regular message to many smokers. Furthermore, Kondo said, patients pay more attention to health-related messages from their doctors than they do messages from the media or from their families. “What physicians say has so much influence on patients,” said Kondo, who provides behavioral change counseling to patients and corporate clients through M. D. Anderson Cancer Center’s LifeCheq™ program. “Just a few words of advice and support can have a great deal of impact.”

Kondo recognizes that the demands on a physician’s time are great, but the counseling techniques that he recommends are simple and can be done quickly. “The goal is not that all physicians should be bang-up counselors,” Kondo said, “but simply that they should say something to their patients who smoke.” He suggests that even specialists, such as thoracic surgeons, who do not normally consider primary prevention efforts their territory have a golden opportunity to influence patients who have diseases caused by smoking.

The National Cancer Institute suggests four ways (all beginning with the letter ‘A’) that smoking cessation counseling can be incorporated into physicians’ practices: Ask patients if they smoke, Advise smokers to quit, Assist patients in quitting, and Arrange for follow-up.

Helping the patient become ready to quit

The first two steps, asking whether patients smoke and advising that smokers quit, only take a couple of

Resources for Smoking Cessation Counseling

- The National Cancer Institute offers a free booklet, “How to Help Your Patients Stop Smoking” (NIH Publication 89-3064). To order it, call 1-800-4-CANCER.

- The American Academy of Family Physicians sells a kit to teach physicians how to counsel their patients about smoking cessation. The kit includes physician and patient handbooks, audiotapes for the physician, and chart stickers. For information, call 1-800-274-2237.

- Agencies such as the American Cancer Society, American Lung Association, and American Heart Association have publications and videos for physicians and for smokers, usually free.

- Several of the pharmaceutical companies that are marketing nicotine replacement therapies provide kits that include the Fagerstrom scale, quit-date contracts, and self-help materials for patients.

- Patients who need additional support can be referred to Nicotine Anonymous chapters or smoking cessation classes at area hospitals. Kondo recommends classes that meet more than once, have realistic claims for success (<50%), and emphasize strategies for staying off tobacco for the long term.
"Some people feel fairly miserable for a while, so you have to encourage them to hang in there."

minutes, Kondo notes. He suggests a supportive, positive approach to advising, rather than trying to scare the patient or inspire guilt. "Respect the individual," Kondo said. "Smoking is a person's right. If you push too hard, you might alienate the patient." The message can be tailored to the individual's health history, Kondo said. For example, a physician might say, "Mary, your bronchitis could really be helped if you quit smoking."

It may take years for a person to become ready to quit, Kondo said. At a "teachable moment," e.g., the occurrence of a respiratory problem obviously associated with smoking, a patient might be more receptive to messages about quitting. Many lung cancer patients are able to give up the habit; in fact, in doing so, they may feel they are contributing to their treatment, Kondo said. In addition, surgeries are followed by a smoke-free period; patients may be able to use the momentum of this forced abstinence to give up tobacco permanently.

Choosing the appropriate quitting strategy

Once the patient has decided to quit, the physician's role is to assist. The physician can help the patient decide whether to cease nicotine use abruptly or to taper off. According to Kondo, quitting "cold turkey" is generally appropriate for individuals who do not smoke more than a pack of cigarettes a day, do not have severe withdrawal symptoms, and feel mentally ready for this approach. Individuals who are heavier smokers, are nicotine dependent (suffer excessive withdrawal symptoms), or don't think they can stop abruptly may prefer nicotine fading (tapering off the number of cigarettes smoked). Physicians can use the Fagerstrom Tolerance Questionnaire to predict nicotine dependence. "The question I use the most is 'When do you have your first cigarette of the day?'" Kondo said. "The shorter the interval between rising and the first cigarette, the more likely the individual is nicotine dependent."

Nicotine-dependent individuals may benefit from nicotine replacement therapy. The nicotine patch and nicotine gum have been shown to increase quit rates by reducing the physical impact of smoking cessation on the patient while he or she makes the behavioral change. Both the patch and the gum are designed to release a steady flow of nicotine into the bloodstream. Behavioral counseling must accompany both therapies, Kondo said. The patient should quit smoking before using the patch or gum.

Once a patient has decided to quit and knows which approach to take, the next step is to set a quit date. Kondo suggests putting the date in writing in a "contract" to encourage the patient to take it seriously. In choosing the quit date, the physician and patient should consider whether smoking is a more important part of the patient's weekday routine or weekend routine, Kondo said. For example, if the individual smokes more on weekends, then quitting on Monday morning allows five nonsmoking days before the time of most temptation.

Kondo recommends encouraging the patient to change brands periodically before the quit date. The rationale of this strategy is that it's easier to give up a brand you find distasteful than to give up your favorite brand. Kondo does not recommend switching to chewing tobacco or snuff as an intermediate step. He tried this strategy himself 20 years ago when he stopped smoking cigars and pipes. "The lungs are better off, but chewing tobacco is terrible for the oral region," he said. "Chewing tobacco can deliver the same amount of nicotine as a cigarette, and you have a new bad habit to break."

Following up

After cigarette use is stopped, the smoker's circulatory system and lungs are cleared of carbon monoxide and nicotine within two to three days, Kondo said. According to a 1991 review by Belgian researchers S. Beckers and Frederic Camu, normal ciliary function returns in four to six days, sputum production decreases in two to six weeks, and immune function improves in six to eight weeks. It may take more than eight weeks for pulmonary irritation to clear up. "Some people can breathe better and have more energy right away," Kondo said. "However, some people feel fairly miserable for a while, so you have to encourage them to hang in there."

Common symptoms of nicotine withdrawal are irritability, insomnia, constipation, difficulty concentrating, lightheadedness, a tight feeling in the chest, and cravings for tobacco. Except for irritability and cravings, Kondo said, these conditions can be expected to last only about two weeks. Weight gain is almost inevitable after smoking cessation, he said, and
"Just a few words of advice and support can have a great deal of impact."

... can motivate some people to start smoking again. He suggests telling patients who quit smoking to step up their exercise routines and watch their diets. If weight gain is a major concern, suggesting that the patient join a group like Weight Watchers for maintenance purposes may even be a good idea, he said.

Seventy percent of people who quit smoking relapse within three months, Kondo said. The physician can help prevent relapse by following up with encouraging messages. If the patient is being treated for a chronic illness, office visits provide an opportunity for these messages. "Unfortunately, visits just for smoking cessation counseling are not reimbursed by most insurance companies," Kondo said, "which is absurd, because so many health problems are associated with smoking." However, a phone call from the physician or from a nurse or staff member takes less than five minutes, he said. "I call on the quit date, two or three days later, and again a few days later to provide reinforcement," Kondo said. "Just the contact means a lot to the patient." He suggests words of support: "How are you doing with your smoking, Joe? How are your withdrawal symptoms? Are you breathing better? Is your illness better since you quit?" Another option is sending a postcard.

The amount of effort put into counseling a patient depends on several factors, like how committed the patient is and whether the patient has a smoking-related condition," Kondo said. "Realistically, smoking cessation counseling is just one of many aspects of the physician's practice." However, with a small investment of time, Kondo believes, physicians can play a pivotal role in encouraging patients to give up tobacco permanently.

—SUNITA PATTERSON

Physicians who desire additional information may write Dr. Al Kondo, Department of Behavioral Science, Box 243, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, or call (713) 792-0919.

Cisplatin Analogue

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of intravenous L-NDDP was started immediately thereafter. The results indicated that the toxic effects of intravenous L-NDDP in humans mirror those of the animal studies: no dose-limiting nephrotoxic effects were observed, but the bone marrow was suppressed. The two phase I-II studies now being conducted at M. D. Anderson will explore the potential pharmacologic advantage provided by liposomes when administered by intrapleural and intraarterial routes.

Although Khokhar and Perez-Soler are quite pleased with the progress of the studies that have been done so far, L-NDDP is still years away from standard application. "The drug development process is very long. It can take 15 years for a drug to go through the necessary studies and regulatory approvals," said Khokhar, who hesitates to estimate when L-NDDP or a drug like it will be available. "We don't like to make predictions. Doing so sometimes gives false hopes. One reason for our success is that we treat these issues very conservatively. Although our results with L-NDDP have been promising, we'll have to wait and see."

Perez-Soler added, "We know that L-NDDP, from a pharmaceutical point of view, is probably not the best compound within the family of analogues we are studying, because it's a mixture of isomers and tends to be unstable within the liposomes; L-NDDP gives us, however, the opportunity of testing the therapeutic concept of a lipophilic platinum compound delivered in a drug carrier, which is a novel idea. Should the current and future phase II studies show that this approach has a real therapeutic value, we may have to substitute one of its isomers or a closely related analogue that has better stability characteristics."

—KEVIN FLYNN

Physicians who desire additional information may write Dr. Abdul Khokhar, Department of Clinical Investigation, Box 52, or Dr. Roman Perez-Soler, Department of Thoracic/Head and Neck Medical Oncology, Box 80, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, or call (713) 792-2837 (Khokhar) or 792-6363 (Perez-Soler).
The proportion of cancer deaths has indeed risen, but some of the increase is due to reduction in death rates from other diseases and a longer life expectancy

Shallenberger agreed that the public perceives the overall risk of cancer to be greater now than it once was, with some justification. He cites discoveries of previously unknown risk factors and carcinogens, which are often widely and sensationaly covered in the popular media, as a major contributor to this perception. It is true that the proportion of cancer deaths in this country has increased in the last 60 years, but the threat of death from many non-cancer-related diseases has been reduced or eliminated, Shallenberger said, so that life expectancy has increased considerably in this century. “Cancer is largely a disease of older people,” said Shallenberger. “There are more and more relatively healthy older people available to develop cancer.”

Shallenberger also said that the methods of collecting data about cancer incidence and mortality, although still far from perfect, have improved significantly, making current data more reliable. However, this creates the appearance that the incidence of cancer, or the number of new cases in a given population during a specified period, has increased more than it actually has. In describing the battle to keep accurate and reliable statistics on cancer risk, Shallenberger also cited the improvements in treatment of several kinds of cancer that have dramatically reduced cancer fatalities. Because cancer mortality is no longer as accurate an indicator of incidence as it once was, it has become necessary to monitor trends in cancer incidence rather than cancer mortality, which because of inefficient record keeping is a much more difficult task.

More sensitive and widely used screening methods detect more cancers, including premalignant lesions

Another factor that makes cancer risk estimation difficult is the effect of screening programs. Today’s more widespread screening programs are causing an increase in reported incidence. Shallenberger cautionned, however, that most of this reported increase should be attributed to greater numbers of people being screened; it is inappropriate to conclude from this increase that there has been an increase in prevalence of the agents that cause these tumors.

Each of these factors in a different way creates the incorrect perception that the risk of cancer is increasing rapidly. “It is not surprising,” Shallenberger said, “that the perception of the relative importance of cancer as a cause of death, along with the steady stream of reports in the newspapers, television, and other media about cancer risks, should lead people to believe that our success in discovering avoidable causes of cancer and improving treatment of cancer is outweighed by the spread of new hazards.” It’s no wonder, said Shallenberger, that “there’s a popular perception that we’re not making progress.”

Probabilities are a better indication of risk than are incidence rates

The probabilities of developing cancer, which are shown on life tables, are sensitive to changes over time in incidence and mortality. Life tables allow us to construct estimates of the changing risk of developing cancer by age, sex, and race. They can be constructed for all cancer sites combined or for individual sites. The development of life tables requires that living individuals who do and do not develop cancer be counted. Because individuals are dismissed when they die of other causes, the life table methodology is sensitive to the reduction in noncancer mortality that changes in incidence rates do not express directly. For example, the lifetime probability of developing prostate cancer is higher for white males than for black males, even though the age-specific incidence rates are higher for blacks than for whites in almost every age group. This apparent contradiction occurs because mortality due to other causes is higher for blacks.

Life Table Sources

To obtain more information on life tables, contact the Surveillance Program, Division of Cancer Prevention and Control, National Cancer Institute, Executive Plaza North, Room 343J, Bethesda, MD 20892-9903. Phone: (301) 496-8510.
What really happened was that, as already cited, the widespread screening; moreover, the method had reported incidence had increased because of more screening and increased detection and treatment of breast cancer, and the chance for a 50-year-old black woman is less than 1 in 12. Some experts, therefore, are now suggesting that risk be framed as the chance of developing cancer in the near future—say, within the next year. When this risk figure is calculated, it is generally much, much lower: about one in 3,700 for a woman in her 30s."

Another misconception that arises from the reporting of these statistics is when the incidence appears to increase. For example, in the early 1980s, before the dramatic increase in mammography utilization, the lifetime risk of a woman developing breast cancer was one in ten. In the space of only a few years, this risk was reported to have increased to one in nine and then to one in eight. This created the perception that millions more young and middle-aged women had been affected over a short period of time. "That’s painfully wrong," said Shallenberger. What really happened was that, as already cited, the reported incidence had increased because of more widespread screening; moreover, the method had changed to account for a longer life expectancy.

**Guidelines for physicians**

The most important thing for a physician to do, says Shallenberger, is to listen when the patient who has no special risk factors expresses an unreasonable amount of anxiety about or interest in cancer risk. Remember that the patient may find it difficult to understand the statistics she or he finds in the media. Since most patients are thinking only of the near future, the next few years, it’s very important that the physician emphasize what the risk is for that patient now. The physician should keep a set of up-to-date risk tables available and use them to show patients their estimated risk based on their age, sex, and race, thus reducing anxiety. The physician should remind fearful patients that these estimates are reliable because they are based on the past experiences of large samples of the population. However, because they refer to averages, they relate to a patient by his or her membership in a group and cannot be used to precisely determine his or her risk. Although these tables should not be applied to people who fall into certain high-risk categories, in most cases the physician will be able to show patients that their risk is much less than they had feared.

Moreover, said Shallenberger, declines in incidence are almost always real. The risk of developing gastric cancer, for example, has dropped dramatically in this country during this century. He does acknowledge, however, that the lifetime risk estimates of developing any kind of cancer were somewhat higher in 1988 than they were in 1980 (about 8% higher for adult white males). Experts suspect that only about one third of this increase is actually due to increased cancer incidence. Another third is attributed to declines in death rates from other diseases, and the final third is thought to be a result of variations in the statistical methodology. Shallenberger chooses to emphasize the positive: he expects that the cumulative effects of better screening and increased detection and treatment of premalignant lesions will eventually reverse the true incidence figures. Furthermore, he urges physicians to remind their fearful patients that much progress has been made in diagnosing and managing cancer and that behavioral changes such as quitting smoking have a profound effect on cancer risk.

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**The much-repeated one in eight risk of breast cancer applies only to white female infants**

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M. D. Anderson's Shallenberger gives three simple guidelines

Physicians can help allay fear by helping patients understand cancer risk

Just about any primary care physician will tell you: more and more patients are aware of cancer risks and increasingly uneasy about their own chances of developing cancer. Patients are bombarded with information about risk factors for different cancers, some of it contradictory, most of it mysterious. They turn to their primary care physicians for advice and reassurance. They want to know, how can I keep from becoming one of these statistics? Young healthy women anxious about breast cancer ask for prophylactic mastectomies. They have heard that one in eight women will get breast cancer, and they do not want to be the one. They are not alone. Men and women in many different age, ethnic, socioeconomic, and occupational groups, similarly fearful about developing cancer, are looking to their primary care physicians for ways to prevent the disease.

Although some of these people, because of their family history or their own medical history, truly fall into high-risk categories, many others do not. Are these fears justified, or is there an epidemic of cancerphobia?

Rick Shallenberger, M.P.H., an epidemiologist in the Department of Patient Studies at M. D. Anderson Cancer Center, believes that primary care physicians can allay their patients' fears—real or otherwise—by understanding the methods used to estimate risk. Armed with this knowledge, physicians can help their patients interpret the statistics and apply them to their own situations. According to Shallenberger, physicians should keep three things in mind when talking to patients about risk. Doing so, he believes, can create a more rational basis for health care and behavioral decision making.