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NON-CIRCULATING

REPORT TO PHYSICIANS

JULY/AUGUST 2002 Vol. 47, No. 7/8

Oncology

New Agents and Strategies Help Oncologists Balance Benefits and Risks of Chemotherapy

by Sunni Hosemann

Since the accidental discovery that mustard gas, an agent developed for chemical warfare, could be used to treat certain types of cancer, oncologists have taken on the uneasy responsibility of meting out powerful drugs to their patients.

Every day, clinical oncologists weigh the risks and benefits of different types of chemotherapy and counsel their patients about the treatment decisions they face. Meanwhile, cancer investigators continue their search for kinder, gentler cures.

Chemotherapy regimens are associated with complications and adverse effects that can increase morbidity and mortality rates, lower quality of life, and raise the economic costs associated with cancer care. Some adverse

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While receiving chemotherapy in the Ambulatory Treatment Center, **Roderick Evans** visits with **Dr. Jessica Hwang**, an assistant professor in the Department of General Internal Medicine, Ambulatory Treatment, and Emergency Care.



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Balancing the Benefits and Risks of Chemotherapy

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events are transient and resolve after therapy is completed. Many can be offset by adjuvant medications and good supportive care. All are of concern because they increase suffering. Of gravest concern, however, are adverse effects that constitute dose-limiting events or cause the therapy to be abandoned. Therefore, research must necessarily focus not only on outcomes such as disease response and survival rates but also on morbidities associated with the drugs themselves. Balancing the therapeutic benefit of a drug against its unwanted effects is common to drug therapies for any disease. But in cancer therapy, it is perhaps more sharply defined because of the aggressive nature of the disease itself and the inherent toxicity of some of the agents used to treat it.

Clinical approaches

"The major challenge is to reduce undesirable effects without losing effectiveness," said Laura L. Michaud, Pharm.D., a clinical pharmacy specialist in The University of Texas M. D. Anderson Cancer Center's Division of Pharmacy, "and there are many strategies and techniques we can use to do that." One strategy is to use adjuvant drugs, such as new and potent antibiotics and antiemetics, to treat or prevent adverse effects. Cytoprotective agents are also used adjuvantly to protect normal tissues—but not tumor cells—from chemotherapy-associated toxicity. For example, dexrazoxane is used to protect against anthracycline-induced cardiac damage. Other examples include mesna, which is used to reduce the toxic effects on the bladder associated with ifosfamide and cyclophosphamide, and amifostine, which protects against kidney and nerve damage that can be caused by chemotherapy and is used primarily in patients with ovarian cancer.

Another strategy is to change the way a drug is administered. For example, the cardiotoxic effects of doxorubicin, an agent used in many chemotherapy regimens, can be offset without compromising the drug's effectiveness by administering it via long continuous

infusion (typically over 48 to 96 hours) instead of by shorter infusion or as a bolus. Similarly, administering paclitaxel in smaller, more frequent doses (weekly instead of every three weeks) appears to reduce the incidence of neurotoxic effects and neutropenia. Giving drugs slowly over time often lowers the incidence of nausea as well, said Dr. Michaud.

She emphasized, however, that such strategies can have some disadvantages. For example, none of these approaches eliminates adverse effects. Instead, each

is chosen because it substitutes milder adverse effects for some of the more serious ones. "We see more fluid retention with the weekly paclitaxel doses," Dr. Michaud said, "and more mouth sores with long infusions of doxorubicin." Sometimes these regimens require more frequent trips to the clinic, which can be inconvenient or difficult for some patients.

Most of these approaches represent techniques specific to particular drugs rather than strategies that can be generalized. For example, not all drugs can be given in smaller doses over a longer time

Intravenous Administration of Busulfan Reveals a Therapeutic Window

Borje Andersson, M.D., Ph.D., a professor in the Department of Blood and Marrow Transplantation, came to The University of Texas M. D. Anderson Cancer Center as a clinical fellow in 1981, excited about the opportunity to pursue research in the treatment of leukemia. "I thought this was the best place in the world to do that, and nothing in my experience since then has convinced me otherwise," he said. He was and still is concerned about toxicity levels associated with chemotherapy, specifically how much toxicity is acceptable.

Dr. Andersson began reviewing data on the probability of survival after allogeneic hemopoietic stem cell transplantation for patients with chronic myelogenous leukemia. The available data showed that the more closely matched the donor, the better the outcome, but Dr. Andersson also recognized that in the first 100 days after transplantation, approximately 20% of all patients died of complications. This was considered an acceptable rate and thought to be independent of the pretreatment regimen for stem cell transplantation.

This pretreatment, or intensive "conditioning" treatment, is given to achieve myeloablation and immunosuppression, which are required to allow engraftment of the transplanted stem cells. The drug busulfan, an alkyl-

sulfonate, is one of the agents commonly used in this conditioning regimen.

When he began investigating correlations between blood levels of busulfan and transplant outcomes, Dr. Andersson recognized that data on blood levels of the drug were not necessarily straightforward and that there was a great deal of variability, even within individual patients. Part of the difficulty was associated with the variability in the absorption and clearance of orally administered drugs, and this was compounded by the fact that almost all patients experienced nausea and vomiting with loss of unknown quantities of the drug. At the time, busulfan was only available as a tablet.

Hypothesizing that an intravenous busulfan formulation would likely yield more predictable pharmacokinetics, Dr. Andersson developed, in collaboration with Diana Chow, Ph.D., an associate professor of pharmaceuticals at the University of Houston, a stable busulfan solution that could be administered intravenously. After extensive clinical trials, authorities in the United States, Canada, Israel, and Korea approved the new drug formulation, and regulatory approval is pending in Japan and Europe. Busulfan plasma concentrations after intravenous administration are very predictable, allowing clinicians to more accurately tailor the dosage for individual patients. This turned out to

without reducing their efficacy. Worse, there are instances in which this strategy could increase the likelihood of tumor cells developing drug resistance. Similarly, while oral preparations of some (but not all) drugs are better tolerated, they may also be more difficult to monitor and titrate, making it harder to optimize their therapeutic effects and minimize their ill effects. Nonetheless, these strategies, used appropriately in the context of other symptom-relieving strategies, can help more patients successfully complete chemotherapy.

Pharmaceutical approaches

Another approach to the problem of toxicity is to chemically alter the drugs' molecules—modifying their formulations or, in some cases, creating different drugs altogether. Liposomal formulations, for example, change the distribution of a drug by targeting tumor cells, which take up the liposome more readily than normal cells do. Doxorubicin and daunorubicin are both available this way, as is a formulation of cytarabine, which is given intrathecally for lesions in the lining of the brain.

Similarly, for some drugs—granulocyte colony-stimulating factor (G-CSF) is one—pegylated (polyethylene glycol-encapsulated) formulations are used so that the drug molecule is not broken down by metabolic processes before reaching its target. While liposomal preparations and pegylation formulation strategies are used mainly to lengthen the duration of the drugs' actions, they may also reduce toxicity to organs by delivering drugs to tumor cells in a more targeted way; this is

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Dr. Borje Andersson, a professor in the Department of Blood and Marrow Transplantation, holds a bottle of intravenous busulfan, which he developed along with **Dr. Diana Chow**, an associate professor at the University of Houston. Unlike its oral formulation, intravenous busulfan is highly predictable, allowing clinicians to tailor its dosage to individual patients.

be very important when comparing data on drug levels in the blood and clinical toxicity. Higher blood levels of busulfan were associated with increased rates of complications such as mucositis, gastrointestinal upset, hepatic problems, and surprisingly, graft-versus-host disease (GVHD). Previously, GVHD had been correlated only to donor match, but Dr. Andersson showed that with all other factors being equal, a more intense busulfan exposure increased the incidence of GVHD and, further, that blood levels of busulfan had a direct correlation with long-term survival after transplantation.

What the data on survival probability relative to busulfan levels suggested was that within a tight range of drug concentrations, myeloablation and engraftment occur optimally, with better disease control, and the survival rates were therefore higher. Busulfan levels above this range were associated with increased toxicity to major organs and a higher risk for serious GVHD; levels below the optimal range were associated with disease progression.

Said Dr. Andersson, "We could now statistically define the optimal level for the drug—a therapeutic window that will enable us to place

every patient inside that window."

Early results of Dr. Andersson's study, which has been accepted for publication in the journal *Biology of Blood and Marrow Transplantation*, are striking: in the initial study of 36 patients, 80% of the patients with busulfan concentrations inside the therapeutic window were alive and in remission four years after transplant, compared with 20% of the patients outside this interval.

The broader impact of such work is that it has strategic implications for delivering individualized chemotherapy. Traditionally, doses of chemotherapy, like most other drugs, are given according to body weight or body surface area, neither of which accounts for individual patient differences in metabolizing or disposing of chemotherapeutic drugs. Intravenous busulfan behaves in such a predictable way that one should be able to predict the clearance of a high dose of the drug based on a low test dose. It should now be possible to predict the optimal drug blood levels for an individual patient using a computer simulation. This novel simulation strategy is more akin to the standard way radiotherapists have calculated and individualized patient treatment for years.

"This finely tailored, individualized approach gives us better disease control and a lesser risk for serious complications with improved patient survival," said Dr. Andersson. "I firmly believe this will be the wave of the future." ●

FOR MORE INFORMATION, contact Dr. Andersson at (713) 794-5743.

Balancing the Benefits and Risks of Chemotherapy

(Continued from page 3)

the subject of ongoing research.

Some newer classes of drugs, while not without adverse effects, are more benign in that regard because they are more targeted to tumor cells. For example, the drug imatinib (STI571), used to treat patients with chronic myelogenous leukemia, targets a specific gene in tumor cells and does not act on other cells, thus causing fewer adverse effects than standard chemotherapy.

Often, an advance may be in the form of a new combination of drugs. The use of the chemotherapy combination ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) in the treatment of Hodgkin's disease is an example. Depending on the stage of disease, ABVD—used instead of or alternating with the previous longtime standard combination regimen MOPP (mechlorethamine, vincristine, procarbazine, and prednisone)—has been shown to result in fewer cases of treatment-induced sterility and

secondary leukemia, while demonstrating the same or improved efficacy.

Hematological support

Damage to blood cells is a common and worrisome complication of cytotoxic chemotherapy, causing anemia and neutropenia that can interrupt or, in some cases, force the cessation of potentially curative treatment. According to Robert S. Benjamin, M.D., professor and chairman of the Department of Sarcoma Medical Oncology at M. D. Anderson, the development of colony-stimulating factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and G-CSF was an important advance. These agents are widely used to speed up neutrophil recovery. The use of G-CSF to help support white blood cells, for example, has made it possible to continue giving therapeutic doses of chemotherapy, avoid reducing the dosage, or in some cases, give higher and more effective doses.

“Certainly, having approaches to support patients through the myelosuppressive phase of their therapy has had an impact in many cancers, but it has been critical for the treatment of sarcoma, where it is necessary to use relatively high doses of chemotherapy,” said Dr. Benjamin.

Whereas G-CSF and GM-CSF have been used successfully to reduce the incidence of neutropenia and the risk of infections in patients receiving cytotoxic treatments, thrombocytopenia has been managed primarily with platelet transfusions and chemotherapy dose reductions, according to Saroj Vadhan-Raj, M.D., professor of medicine and chief of M. D. Anderson's Section of Cytokines and Targeted Therapies in the Department of Bioimmunotherapy.

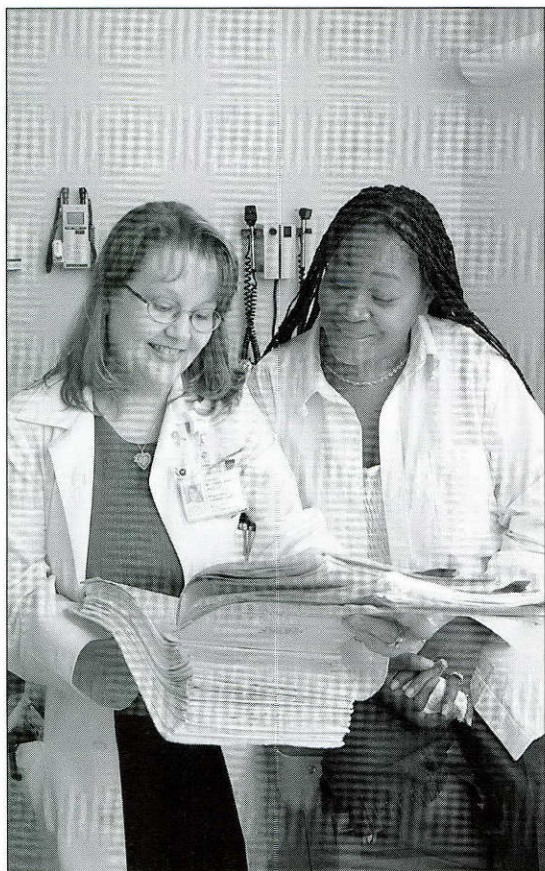
Dr. Vadhan is working with recombinant human thrombopoietin (rhTPO) to ameliorate thrombocytopenia associated with intensive chemotherapy

The search continues for ways to make chemotherapy more tolerable, but years of hard work and research in countless laboratories and clinics are tipping the scales in favor of patients.

in patients with gynecologic malignancies or high-risk sarcoma. In early clinical trials at M. D. Anderson and elsewhere, thrombopoietin has shown very potent platelet-stimulating activity in patients with cancer.

“Despite the promising results and excellent safety profile, however, the clinical development of this platelet growth factor has been very slow, in part because rhTPO has a delayed peak response and is not consistently effective when given after chemotherapy,” Dr. Vadhan said. “We have now shown, in a recent trial in patients with sarcoma receiving intensive chemotherapy, that only two doses of rhTPO—one dose given a few days before chemotherapy and one dose given after chemotherapy—were effective in abrogating severe thrombocytopenia.” Randomized, double-blind clinical trials are ongoing to determine the safety and efficacy of this agent in patients at high risk for severe thrombocytopenia.

The search continues for ways to make chemotherapy more tolerable, but years of hard work and research in countless laboratories and clinics are tipping the scales in favor of patients. ●



Dr. Laura L. Michaud, a clinical pharmacy specialist in the Division of Pharmacy, meets with patient **Annie Richardson**.

FOR MORE INFORMATION, contact Dr. Michaud at (713) 792-4552, Dr. Benjamin at (713) 792-3626, or Dr. Vadhan at (713) 792-7966.



Exercise Improves Quality of Life for Patients with Cancer

The recommendation to exercise during a serious illness may come as a surprise to some, but the assertion in the title of this House Call is true. Recent studies show that moderate exercise after a diagnosis of cancer can help alleviate some psychological symptoms and help maintain or improve physical functioning during treatment and afterward.

In addition to its general benefits, exercise has been shown in some studies to reduce nausea and fatigue, symptoms that occur in up to 70% of patients undergoing chemotherapy or radiation therapy. Exercise may help boost the body's natural defense system (immune system) and help stimulate the appetite. Regular exercise also may help you feel less dependent on others for help with your daily activities.

Finding the Right Type of Exercise

Although more studies need to be conducted to determine the best level of exercise for patients with cancer, the exercise you choose should be an activity that is aerobic (works your heart) and that you enjoy. You could, for instance, take a walk, ride a bike, go for a swim, mow the grass, wash the car, or work in your garden. If you prefer to be indoors, consider taking the stairs instead of an elevator when you can, use an exercise machine, or simply play with your children or grandchildren.


Scheduling Time to Exercise

For patients with a chronic illness, the American College of Sports Medicine recommends 20 to 60 minutes of moderate exercise at least three days a week. If you have limited mobility or need assistance to exercise, start with just five minutes at a time, slowly

General Benefits of Exercise

- + Improves physical capacity
- + Maintains muscles, bones, and joints
- + Reduces depression and anxiety
- + Improves self-esteem
- + Prevents osteoporosis
- + Lowers risk of obesity
- + Increases energy
- + Decreases risk of heart disease
- + Lowers blood pressure
- + Reduces cholesterol
- + Decreases risk of diabetes

= Better Quality of Life



working your way up. You can also divide your exercise time into shorter sessions with breaks in between. The more you exercise, the easier it will become because your stamina will increase.

If you are fatigued as a result of your cancer treatment, the American Cancer Society still recommends light to moderate exercise when you are feeling up to it, perhaps at times during the day when you are feeling your best. Even if you are receiving home care, try to stay as physically active as possible by doing as many things for yourself as you can and, if necessary, by having someone help you exercise your joints.

Consulting Your Doctor

Certain medical conditions or treatments may limit the amount or type of physical activity you can undertake, so always consult your doctor before beginning an exercise

program. And remember, exercise only as much as you can at a time. If you experience severe pain, rapid heart rate, breathlessness, headaches, blurred vision, or numbness or tingling in any part of your body, stop the exercise and consult your doctor. The most beneficial exercise programs are those that remain safe and enjoyable. ●

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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Prevention, Early Diagnosis, and Effective Therapies Are Keys to Controlling Infections in Patients with Cancer

by Don Norwood

Controlling infections is important at any medical institution, but at cancer treatment and research facilities such as The University of Texas M. D. Anderson Cancer Center, it is crucial. Patients with cancer, particularly bone marrow transplant recipients and those with leukemia, require a comprehensive approach to infection control that focuses on the early diagnosis, prevention, and treatment of infections in both patients and hospital employees.

"Patients with cancer become susceptible to infections through different routes," said Issam I. Raad, M.D., professor and ad interim chair of the Department of Infectious Diseases, Infection Control, and Employee Health. "First of all, they can become immunosuppressed as a result of their underlying disease. The best example of this situation is leukemia patients, where the tumor involves the white blood cells. In patients with solid tumors, the tumor may obstruct a certain airway or duct, thereby leading to infection. An example of this would be patients with thoracic cancer in whom there is a bronchial obstruction."

Patients who receive chemotherapy also are susceptible to infection. One of the major complications of chemotherapy is that it is immunosuppressive in most cases, often producing bone marrow suppression, which results in a low neutrophil count and affects other white blood cells, such as

"Number one, patients can prevent infections by maintaining a high level of hygiene....

Number two is earlier reporting to their physicians and emergency center if they develop fever....

Number three is complying with [the recommendations of] their primary physician ..."

– Issam I. Raad, M.D., professor and ad interim chair, Department of Infectious Diseases, Infection Control, and Employee Health

lymphocytes and macrophages.

The third pathway for infections in patients with cancer is through devices, catheters in particular, that deliver chemotherapy, antibiotics, fluids, or total parenteral nutrition. "What catheters do," Dr. Raad said, "whether they are nephrostomy tubes, vascular catheters, or urinary catheters, is connect a contaminated area with a sterile environment. The best example is central venous catheters. They connect a skin-contaminated area with the sterile bloodstream. This leads to the migration of organisms from the skin, along the catheter, and into the bloodstream."

Given the widespread use of catheters in patients with cancer, the Department of Infectious Diseases, Infection Control, and Employee Health has made a substantial contribution to the prevention of infections in this population through the development of catheters impregnated with antimicrobial agents. This innovation effectively neutralizes one of the three major

infection pathways. Dr. Raad said that a future adaptation of this technology would be catheters impregnated with antiseptic agents.

The department is working closely with the Centers for Disease Control and Prevention and Memorial Sloan-Kettering Cancer Center, Fred Hutchinson Cancer Research Center, and Johns Hopkins University, having established a network among these institutions for consultations and to exchange ideas about the prevention and management of infections. This interaction will be crucial as oncologists face infections associated with new treatment modalities and more intense chemotherapy.

A major concern is the emergence of organisms that are resistant to multiple antibiotic and antimicrobial agents. According to Dr. Raad, the more nontoxic an antimicrobial agent is, the more likely it is to be misused and overprescribed.

"I think we have to think creatively in the future," he said. "We can shape



the future by focusing on the infections associated with the highest morbidity and mortality rates. Next, we must work out creative strategies to minimize the risk of infection without creating the monsters of multidrug-resistant organisms. We also have to think of the potential use of innate antimicrobial peptides for infections that are not predisposed to antibiotic resistance.”

As part of their efforts to meet the challenges Dr. Raad described, researchers have been testing several novel antibacterial agents. In particular, Gerald Bodey, Sr., M.D., a clinical professor in the Department of Infectious Diseases, Infection Control, and Employee Health, is studying third-generation cephalosporins and antipseudomonal penicillins, which have become the standard of care in the treatment of patients with high-risk neutropenia. Kenneth Rolston, M.D., a professor in the department, has developed an outpatient treatment strategy for patients with low-risk neutropenia.

In an effort led by Dr. Raad and Dr. Rolston, anti-gram-positive antibiotics, such as quinupristin and linezolid, are being tested in patients who have infections that are resistant to conventional therapy. Finally, and most recently, is the breakthrough in the development of echinocandins and triazoles, which are used to treat fungal infections in immunocompromised



According to **Dr. Issam I. Raad**, creative strategies for the use of antibiotic and antimicrobial agents are needed to prevent the development of drug-resistant organisms.

Studies Look for Better Ways to Treat Infections in Patients with Cancer

Among the research efforts under way at The University of Texas M. D. Anderson Cancer Center are the following clinical trials of strategies for the treatment of infections in patients with cancer.

- A pilot study of once-daily, oral, outpatient antibiotic therapy in patients with low-risk febrile neutropenia (ID00-376). *Physician: Kenneth V.I. Rolston, M.D.*
- A randomized, double-blind, phase III comparative study of daptomycin and linezolid in the treatment of hospitalized adults with suspected vancomycin-resistant enterococcal infections (ID01-204). *Physician: Kenneth V.I. Rolston, M.D.*
- Risk-based management of fever and neutropenia in pediatric patients with cancer (P98-132). *Physician: Craig Mullen, M.D., Ph.D.*
- A randomized, double-blind trial comparing linezolid with vancomycin in the empiric treatment of patients with febrile neutropenia and suspected gram-positive infections (ID01-507). *Physician: Kenneth V.I. Rolston, M.D.*
- Linezolid in the treatment of penicillin-resistant streptococcal pneumonia: an open-label, noncomparative study (ID01-463). *Physician: Kenneth V.I. Rolston, M.D.*
- An open-label, noncomparative study of the safety and efficacy of intravenous anidulafungin plus amphotericin B as a treatment for invasive aspergillosis (DM02-003). *Physician: Issam I. Raad, M.D.*
- A pilot validation study of the Febrile Neutropenia Symptoms and Activities Questionnaire, a new health-related quality-of-life instrument to be used in a clinical trial involving patients with cancer who have fever and neutropenia (DM01-241). *Physician: Kenneth V.I. Rolston, M.D.* ●

patients. Dimitrios Kontoyiannis, M.D., an assistant professor in the department, and Dr. Raad spearheaded this research.

Patients themselves and those who care for them also can do a great deal to prevent and treat infections, said Dr. Raad. “Number one, patients can prevent infections by maintaining a high level of hygiene. I mean hand washing, good care of their catheters, etc.,” he said. “Number two is earlier reporting to their physicians and emergency center if they develop fever, particularly if they are neutropenic. Number three is complying with [the recommendations of] their primary physician not only in reporting infections at an early stage but also in prevention, including vaccinations when appropriate and avoiding close contact with people who have

an infection.”

Emphasizing that the department’s focus in the future will remain firmly on the eradication of infections in patients at M. D. Anderson, Dr. Raad said that this goal will require a comprehensive approach.

“We have to be diligent in all three areas: early diagnosis, prevention, and pre-emptive therapy, with the target being saving the lives of patients,” Dr. Raad said. “We have to make ourselves available, particularly to the patients at highest risk—that is, patients with leukemia, bone marrow transplant recipients, and critically ill patients—without forgetting the needs of patients with solid tumors, including surgical patients.” ●

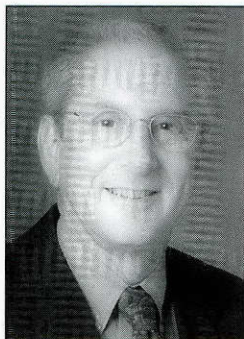
FOR MORE INFORMATION, contact Dr. Raad at (713) 792-7943.

DiaLog

Why Refer Patients to a Major Cancer Center?

Martin N. Raber, M.D.
Professor of Medicine

Physicians are understandably ambivalent about referring patients to a large cancer center. Poor communication between the center and the referring physician, loss of control over their patient's care, and disagreement over therapeutic decisions can and do occur. Sometimes, consultation calls into question the referring physician's workup and treatment plan, leaving the patient confused about what *should* be done and suspicious about what *has* been done. Despite these concerns, the benefits of receiving treatment in a large center are myriad.



However, not all patients with cancer can be seen at major centers, so we must carefully consider who should be referred for care. I call the underlying principle that I follow "*Right Time, Right Place.*" That is to say, a patient should be treated in a setting that provides the appropriate expertise for the care required in the most convenient (and cost-effective) location. Patients should be referred to a major center when they need more expertise than the community setting can provide. This expertise usually comes from teams of specialists in a single disease or a small group of diseases.

Who should be sent to these specialists? I think first of patients with less common cancers. Study after study has shown that

facilities or teams that treat a high volume of cases generally have better outcomes. I also include in this category patients with unusual manifestations of common malignancies. When all the pieces do not fit neatly together, a specialized team with wider experience is likely to make more sense of a complicated situation. Often, a patient can benefit greatly from new technologies, as well as from the expert review of pathologic material and imaging studies, that are available only at large centers. Physicians can access these services even if the patient is not going to be treated at the center.

Another group that would benefit from referral to a large center is patients with cancers that do not respond well to conventional therapy and for which investigational therapy is available. The opportunity for such a patient to participate in a clinical trial should not be missed. Patients can and do respond to new therapies. The cost in terms of patient dislocation and increased monitoring may be high, but the rewards can be great: giving hope, prolonging life, and contributing to our scientific knowledge.

Finally, I think of patient choice. Cancer is always a serious diagnosis, and patients should be encouraged to seek second opinions. Traveling to another city for care is never easy, but it can be life-saving. In the end, patients and families should feel that they have had every opportunity to pursue all reasonable options for cure. Given the increasing number of patients with cancer and the relatively limited resources available, we all need to work to develop systems that better transfer information and ideas and to truly collaborate in the delivery of patient care.

OncoLog

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