Treatment Team Addresses Needs of the Dying Patient

Despite the progress made in cancer treatment, for some cancer patients disease has advanced too far for cure or no cure is available. Neurosurgeon Richard Moser, M.D., sees patients who have had to face this hard fact, and he is concerned about the quality of the months and weeks that remain for them. Some have become alienated from family members; others worry about the financial burden that health care has placed on the family. For many, the physical and the emotional pain associated with death can be overwhelming.

It is critical that all members of the treatment team attempt to address the physical, emotional, and psychological needs of the terminally ill. Depending on the type of support these patients are given, dying can be a time of reconciliation and peace, or it may mean despair and pain.

"With all the opportunities we've created for ourselves in our society, we've also created many more stresses. Dying is a time of tremendous anxiety for many people," said Moser, who is deputy director in the Department of Neurosurgery at The University of Texas M. D. Anderson Cancer Center. When efforts to cure the patient have become futile, he helps the patient and family accept the fact of imminent death. "This is the most important thing going on in that family's life," Moser said. "I can certainly make it important to me."

Facing death is an awesome task for anyone, admits Porter Storey, M.D. Storey is director of The Hospice at the Texas Medical Center, a facility to which some M. D. Anderson Cancer Center patients are referred when they opt for hospice care. Even health care providers can have difficulty accepting the fact that the patient’s death is approaching, said Storey, who is also adjunct assistant professor of medicine in M. D. Anderson’s Department of Medical Oncology. Preparing for death reflects "neither resignation on the part of the patient, nor defeatism or neglect on the part of the doctor. It is the unique period in the patient’s illness when defeat in living can be gradually converted into a positive achievement in dying," Storey said.

Storey has strong feelings about providing the patient with "honest information" about the terminal prognosis. "Usually it is obvious to the patient that he or she is getting worse," he said. "To encourage the patient to hang on to that 'one chance in a thousand' is rarely helpful, and adds to the 'conspiracy of silence' that leaves the patient feeling isolated and alone."
The Concept of Total Pain

Helping the patient accept imminent death and averting the conspiracy of silence requires a concerted effort by a team of health care professionals. Social worker Gail Eldridge, M.S.W., is an M. D. Anderson treatment team member who helps the patient and family through this time of crisis. The health care team can be most helpful, she said, if they understand and address the fear, guilt, and false hopes that patients and families experience.

These feelings all play a role in the patient's “total pain”—a concept that Eldridge feels all health care professionals must understand. In addition to the physical pain, cancer patients experience many emotional and psychological problems that exacerbate the overall feeling of being in pain. When all sources of pain are addressed, a more peaceful death is possible. “But you can’t talk about the total pain concept without first addressing physical pain,” Eldridge emphasized. “All these other pains are superseded by physical pain. That has to come first not only for the patient but for the family too. Family members cannot address the emotional and psychological pains if their loved one is in physical pain.”

Providing Comfort through Symptom Management

But how to best alleviate physical pain has traditionally been wrapped in uncertainty. Because of fears that the patient might become addicted to pain medications, standard pain relief consisted of conservative dosages. Physicians, however, are increasingly realizing that these concerns are unwarranted (see “Narcotics and Pain Control,” OncoLog, Vol. 33, No. 3, 1988). According to Moser, it is essential to titrate to need. “You can test drug levels, but because people metabolize these drugs differently, those tests will never provide adequate results.” Moser cautions that, with certain cancers, the amount of pain medicine required is so great that it can impair cognitive function; nevertheless, pain relief can be achieved if the dosage is closely monitored.

“I tell patients that they don’t get a merit badge for suffering,” said Moser. He finds that in some cases involving extensive metastasis palliative surgery may be an option, thus reducing the need for high doses of pain medications. "Sometimes the best solution is to fix the problem, not cover it over with medicines.”

Because pain can be such an overwhelming part of cancer in the later stages, Storey has also learned much about pain management. He has found that oral morphine or other oral analgesics are most effective in relieving pain symptoms in 80% of his patients. He describes an adequate dose as one that lasts four hours, and he recommends that one dose be given before the last has worn off. In this way, a constant level of analgesic is maintained in the bloodstream at all times, so the patient does not experience severe pain between doses.

Storey said that his medical training in pain management is typical of that given most physicians. “Most doctors are not familiar with the large doses that are often needed to treat cancer pain, and are quite hesitant to prescribe enough medicine to do the job,” said Storey, who advises physicians to “dose to effect” and to use feedback from other caregivers to help monitor the effectiveness of pain medications.

Symptom Control through Subcutaneous Infusion

Some patients experience severe dysphagia, intractable vomiting, complete gastric stasis, bowel obstruction, or other crises. In such cases, oral medications are intolerable. Storey recommends subcutaneous infusion rather than suppositories for these patients. “We find virtually 100% patient acceptance of subcutaneous infusions, unlike suppository use, among those who cannot tolerate oral medications. Morphine levels from subcutaneous infusions are as high as from intravenous infusions—even in hypotensive patients.”
Storey said that a number of narcotic analgesics can be administered subcutaneously, but only morphine and hydromorphone are effective for subcutaneous infusion. Hydromorphone is six times as soluble as morphine on a weight-per-volume basis, and it takes about 7 mg of parenteral morphine to reach the analgesic potency of 1 mg of hydromorphone. Since the subcutaneous tissue has a limited capacity to absorb fluid, hydromorphone is better if there is a need for very high doses of narcotic or very low volumes of drug (as in multiday infusions). Storey rarely finds that patients require subcutaneous hydromorphone doses over 200 mg/day, although others have reported a range of doses from 40 to 4024 mg/day.

Subcutaneous infusion has also been extremely effective in controlling nausea and vomiting. When oral tablets cannot be tolerated, standard rectal suppositories often provide relief. However, the limited dosage flexibility and frequent turning of the patient limit the usefulness of suppositories. Because chlorpromazine and prochlorperazine are too irritating to subcutaneous tissues, they are not used. There are, however, five antiemetics that are extremely useful: haloperidol, metoclopramide, methotrimeprazine, cyclizine, and hydroxyzine.

Providing Comfort through Counseling

Once the physical pain is addressed, the health care team should then focus on psychological and emotional pain. How these issues are approached often depends on the number of losses the patient and family have already endured, Eldridge said. “How long has this disease been going on? How many changes have they had to make because of it?” are key questions. Have they started off in middle class and are now in poverty because of the financial drain? Have family members become alienated? Are there young children at home? What will happen to them? Have they made peace with their religious beliefs? How about their feelings concerning the hereafter? All these elements can contribute to an overwhelming feeling of pain, Eldridge said.

“Fear plays a big role in this,” she said. She encourages patients and family members to begin talking about their fears and express their emotions. The moment she first meets the patients, Eldridge attempts to get them to talk about the issues behind the fear. She also assists patients in identifying communication problems with families to help them reconcile their differences.

One disconcerting attitude she finds is the one that cancer is a form of “almighty” punishment. “Some people feel that the patient is dying from cancer because of some sin they’ve committed,” Eldridge said. She, along with a hospital chaplain, must help these patients and families separate their religious convictions from their core spiritual beliefs. They may be accepting a dogma that teaches the image of a negative, wrathful God and have never really explored their innermost feelings concerning life and death. Some patients may have religious beliefs that are different from those of their families. “They struggle over these convictions,” she said. “These are big issues.”

Eldridge finds that it is very difficult for patients with advanced disease to realistically maintain hopes of cure.

The family “must know how much nursing care will be required and decide how much they can handle.” — Rozas

“So often, after some response to chemotherapy, the patient’s hopes rise, and he or she begins to think the doctor was wrong, that they’ll be the one to beat this. I work to keep their hopes realistic and their lives full.”

Holistic, Quality-of-Life Approach is Essential

As patients and families face these issues, Eldridge can take steps to solve some financial and social problems. As a social worker, she works with community resource agencies to ensure that patients’ outpatient needs are met. “If you take a holistic, quality-of-life approach to care of the dying, you see that there are so many things that can be done to make life better for them.” It can mean calling the children’s school counselor to explain a parent’s condition. It can mean making arrangements for the patient’s discharge, such as calling churches to see if a member can help with respite care; arranging for Meals on Wheels; procuring equipment such as hospital beds or oxygen; or arranging transportation from hospital to home.

For one family with no insurance and very little income, she referred them to the Texas Department of Human Services for food stamps and to the Social Security Administration to apply for disability income and Supplemental Social Security Income. With those resources established, the family qualified for state-funded Medicaid. Without this assistance, the patient would

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have had a difficult time managing the obligatory blood tests needed in order to continue chemotherapy and would not have qualified for the support services she later needed for in-home care after discharge. M. D. Anderson's Department of Social Services funded an ambulance transfer to get her back home, where she wanted to be in her last days.

Obviously, some problems are not solvable, said Eldridge. It then becomes important to help patients accept the decisions that were made and accept the priorities that were then and are still being set. Sometimes there are value conflicts because the limited amount of money that was available was spent on health care that did not work. “You can’t ‘Monday morning quarterback’ a decision made two years ago that set the ball in motion,” Eldridge said. “That’s part of coming to grips with dying.” To provide perspective on the situation, she sometimes asks a patient to consider what would have been done if their spouse had faced the same prognosis. “They always say, without hesitation, that they would have given it their best shot.” This counseling approach helps them put aside some of the guilt they feel.

“When it comes to providing care, the key is the patient. The patient's needs are the priority, not the money.” — Eldridge

Providing Continuity of Nursing Care after Discharge

The nursing care that is required after discharge is coordinated largely by nursing staff. Patients require various degrees of nursing care, and it is up to the discharge planning nurse to help the family determine whether care can be provided at home, whether outside agencies will be needed as intermittent support services to home care, or whether an inpatient facility will be necessary. “We present the family with the options and help them decide what is best for the situation,” said discharge planner Joye Rozas, R.N.

Before a family decides to attempt in-home care, “they must know just how much nursing care will be required and decide how much they can handle,” Rozas said. So that the family member or caregiver will feel confident with the patient at home, M. D. Anderson provides regular classes on such basic care skills as monitoring bowel and bladder function, mouth care, infection recognition, skin care, fluid balance maintenance, and chemotherapy administration. A detailed outline of care instructions is also provided. The patient is discharged only when staff feels comfortable that the family can provide in-home care, Rozas said.

In some cases, nursing support services provided by home health care agencies will be necessary to assist families in providing care. The discharge planning staff matches the patient’s needs with an appropriate agency. Such home support agencies as the Visiting Nurse Association have long provided various services for dying patients in some communities. A visiting nurse can check vital signs, monitor medication, and change dressings. Home health aides are also available to shampoo hair, bathe the patient, and take care of personal needs.

With in-home care, health care costs are reduced, and the patient receives the emotional support that is so important for terminally ill patients. According to Storey, “it is remarkable how much medical care can be effectively handled at home if the resources are available.” In order to provide effective care, symptoms must be well controlled by simple means, usually tablets or suppositories. Also, families must get enough professional support to allow them to be effective caregivers.

Inpatient Hospices Available

Inpatient facilities such as nursing homes are sometimes an option when the nursing needs are more intensive and when the patient has a funding source. Patients are only referred to agencies that are approved by the patient’s funding source—whether Medicare, Medicaid, or insurance.

Unfortunately, many health care providers do not specialize in problems of the dying cancer patient and thus have difficulty determining the kind of medical care to administer, Storey said. Some patients may receive too much acute care and spend their final months recovering from “futile attempts to stop their advanced illness.” Other patients may suffer from too little attention to their pain, nausea, or dyspnea.

In the past decade, growing numbers of health care practitioners have become aware of the advantages of hospice care as an option for the dying patient. Hospice care professionals are dedicated to controlling
these distressing symptoms and also addressing the patient’s emotional concerns. This allows a cancer patient’s final days to be some of his richest, Storey said. The structure of hospice programs varies considerably. Among the 1400 hospices in the United States today, the majority provide a range of nursing support services for patients dying at home; only 35 hospices offer their own inpatient facilities that provide a caring environment in which the physical and emotional needs of the terminally ill can be met. Other hospice programs have contracts with hospitals and nursing homes to provide hospice care.

The hospice home care arrangement is similar to any in-home care setting, in which family provides the basic patient care; however, supportive nursing services are usually provided by a health care agency with professionals trained in the needs of the dying. Social workers are available to provide counseling and address the psychological and emotional concerns of the dying. Hospice nursing staff also are better trained in attending to the pain needs of these patients.

There are situations in which in-home care just does not work, Storey said. Inpatient hospice facilities have been developed for patients whose symptoms have grown beyond the capabilities of the family. While inpatient hospices provide medical assistance for symptom control, “more medical technology is not necessarily considered to be better. People don’t want to see their family members die in the intensive care unit with all sorts of tubes in place,” Storey said. Inpatient hospices are generally described as “loving, home-like” facilities where social workers and nursing staff focus their attention on making the patient comfortable. At The Hospice at the Texas Medical Center, for example, a comprehensive team approach to hospice care has been implemented. When nurses, social worker, chaplain, home health aides, bereavement counselor, and volunteers all get involved with the patient and family, it is possible to more completely address all the patient’s needs, Storey said.

The Future for Care of the Dying

Health care professionals such as Moser, Eldridge, Rozas, and Storey all advocate the holistic approach to care of dying patients. Though hospice programs are not yet available in every community, their numbers are growing. “There are some pretty innovative hospice-oriented programs available in nursing homes,” Eldridge said. “Hospice, after all, is not a place, it is a care approach.” Many more home health agencies have adopted the holistic approach.

Eldridge perceives a lack of community resources for the patient who is undergoing palliative treatment and is expected to live longer than six months. Very often, she said, that person does not qualify for hospice care, yet needs the type of symptomatic/supportive care that hospices provide. She would also like to see more services made available for indigent patients who are dying. The discharge planning team encounters patients who have no insurance, do not qualify for Medicare or Medicaid, and sometimes have no family to depend on for even minimal care. Nursing homes and many home care agencies will not accept patients without some form of financial support. And some patients are from small rural communities where quality health care resources are at a minimum.

When all sources of pain are addressed, a more peaceful death is possible.

Rozas recalls one patient who had undergone extensive head and neck surgery and was returning home for care. Both his income and the community resources were limited, so his wife accepted responsibility as caregiver. Before he was discharged, she received training from M. D. Anderson staff to provide basic nursing care. However, it became clear to her and to the nursing staff that she would not be able to handle all his care needs. They had no insurance and qualified for neither Medicare nor Medicaid, so an inpatient facility was out of the question, and research conducted by the discharge planning staff revealed that community home health care resources were nonexistent.

“These patients can ‘fall through the cracks’ unless the entire treatment team—social worker, physical therapist, dietitian, clinical nurse specialist, chaplain—tackles the problem of developing a plan for the patient’s discharge,” Eldridge said. In this case, an M. D. Anderson chaplain contacted a local church, who in turn found a volunteer who could help. The patient’s emotional fears then began to surface. Both he and his wife did not want a stranger to see him because of his facial disfigurement. Rozas counseled and reassured them, and they finally accepted the help; “We don’t ever give up,” she concluded.

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effective chemotherapeutic agents, have slowed progress in treatment research. "Frequently, CLL is diagnosed in patients who are in their 70s or 80s. These patients are already susceptible to other fatal conditions such as stroke, heart failure, or second cancers, so they die of other diseases," Keating said. "And because CLL grows slowly, many patients may live eight to ten years, even without treatment, so it takes at least that much time to gather any meaningful survival data."

**Fludarabine as Effective as Multiagent Protocols**

Whether fludarabine will play a role in curative regimens thus will require several more years of research; nevertheless, patients now have an alternative to standard CLL therapy, which usually consists of several courses of alkylating agents such as chlorambucil or cyclophosphamide, sometimes combined with prednisone or vincristine. Standard therapy has induced partial response rates as high as 75%, but disease recurs and patients become resistant to further therapy. Median survival after treatment for advanced disease averages five years.

One encouraging aspect of fludarabine is that it is just as effective in inducing remission as standard multiagent protocols and is less toxic. Keating and his colleagues recently reported a 79% response rate in 33 previously untreated patients (Nouvelle Revue Française D'Hematologie 30:461-466; Journal of Clinical Oncology, in press). They received 30 mg/m²/day of fludarabine for five days every four weeks, and 11 of them (33%) achieved a complete response. In 20% of the courses, patients developed infection or fever, but in terms of other side effects, fludarabine was remarkably nontoxic. There was no evidence of neurotoxicity, and patients did not experience nausea, vomiting, alopecia, or diarrhea.

But perhaps more important is fludarabine's effectiveness in previously treated patients. Keating and his team have also treated 68 patients who had received prior cytotoxic chemotherapy. Patients initially received 25 mg/m²/day for five days every three weeks, but the dosage was later revised to 30 mg/m²/day for five days every four weeks. Of the 39 patients who responded (57%), nine achieved a complete response (13%). This response rate of 57% was a marked improvement over multiagent protocols, whose response rates generally range from 25 to 30%.

**Hope for Patients under the Age of 55 Years**

Consequently, previously untreated patients can now choose a less toxic but equally effective form of therapy, and previously treated patients can elect treatment that is not only less toxic but more effective than conventional regimens. Moreover, fludarabine may provide hope to a subset of CLL patients who at present have no curative treatment options: patients under the age of 55 who have early stage disease.

"It is frustrating that there is no treatment for early stage CLL (elevated white cell count with no evidence of enlarged lymph nodes, liver, or spleen and no evidence of bone marrow failure)," Keating said. "In fact, some studies have shown that immediate treatment of CLL with chemotherapy actually decreases survival because patients develop second cancers. We therefore must defer treatment until the disease progresses."

What do you tell a 40-year-old patient who has a disease that will kill him within eight to ten years, and yet his disease is usually not treated until it gets worse? The answer may lie in combining fludarabine with autologous bone marrow transplantation.

"I think that will be a very important direction," Keating said. "CLL cells can be distinguished from normal bone marrow cells by using monoclonal antibodies. After inducing remission with fludarabine, we could then extract the marrow, use monoclonal antibodies to purge the marrow of leukemic cells, and store it for future use. So for patients under the age of 55 years with early stage disease, this approach may be one way of altering CLL’s inevitably fatal course."

Fludarabine with autologous bone marrow transplantation may also play a role in overcoming another major obstacle to curing CLL: revitalizing the immune system, which is permanently damaged even if chemotherapy induces a response.

"CLL carries a double threat: the malignancy itself and the immune deficiency. CLL severely impairs the function of humoral immunity (mediated by B cells) and cellular immunity (mediated by T cells). We know that the B cells are impaired because the level of antibodies in the serum is low, but trying to isolate the role of T cell impairment has been much more difficult," Keating said.
With most chemotherapy, low neutrophil counts correlate with febrile episodes, but this is not the case with CLL patients treated with fludarabine: Neutrophil counts are often normal when febrile episodes occur. This would suggest that infections are not related to myelosuppression and perhaps are solely attributable to the B cell deficiency. However, the spectrum of infectious pathogens—Pneumocystis carinii, cytomegalovirus, herpes simplex, herpes zoster—seen in fludarabine-treated CLL patients is perplexing. “These infections are more indicative of an abnormality in T cell immunity, such as that seen in acquired immune deficiency syndrome. Something seems to be going on with the T cell immunity, but at present it’s a black box.”

The Next Step: Rebuilding the Humoral Immune Response

Nevertheless, Keating said that researchers are now poised to tackle the problem of restoring the humoral immune response, and to do so they plan to use fludarabine in conjunction with autologous bone marrow transplantation and with cytokines such as interferon, interleukin-2, and interleukin-4. “The good thing about fludarabine is that it can eliminate all or part of the disease in a large number of patients. This has opened up the next dimension of research. Previously, we had no treatment that could reproducibly eradicate the leukemic cells, but now that we do, we have the opportunity to restore the immune response too.”

Fludarabine research at the M. D. Anderson Cancer Center is progressing along several lines. Animal studies have examined a form of fludarabine that can be given by mouth. “If the initial results can be applied to man, then patients will be able to take the drug much more easily,” Keating said. Other phase I and II studies will examine combining fludarabine with chlorambucil, doxorubicin, cytosine arabinoside, mitoxantrone, and interferon.

Fludarabine Also Effective in Other, Rarer Diseases

Keating added that in addition to CLL, fludarabine is showing promise for treating other diseases. “A preliminary study has shown that fludarabine was active against Waldenstrom’s macroglobulinemia (5 of 11 patients responded) and prolymphocytic leukemia (6 of 17 patients). Other studies have shown a 62% response rate (13 of 21 patients) against follicular lymphoma, a 33% response rate (4 of 12) against small cell lymphocytic leukemia, an 80% partial response rate (4 of 5) against follicular mixed cell lymphoma, and a 100% partial response rate against follicular large cell lymphoma (2 of 2).”

Keating stresses that the results are preliminary and the study samples small; nevertheless, they point to fludarabine’s versatility and suggest that in years to come this agent may play a significant therapeutic role in a variety of diseases.

Fludarabine is still considered an experimental drug, so its availability is restricted to research institutions like M. D. Anderson, but in certain cases physicians can acquire the drug from the National Cancer Institute through a “class C” mechanism. “We obviously feel that a patient would benefit from our expertise at M. D. Anderson, but it’s important for physicians to know that, for patients who cannot come or do not want to come to our institution, fludarabine can be obtained from the National Cancer Institute. So for patients refractory to conventional CLL therapies, fludarabine is a viable and accessible treatment option, regardless of where that patient lives.”

Physicians who desire additional information may write Michael J. Keating, M.B., B.S., Department of Hematology, Box 55, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030. Made possible by a gift from the late Mrs. Harry C. Wiess and grants from The University Cancer Foundation.
When listening to Michael J. Keating, M.B., B.S., talk about fludarabine for chronic lymphocytic leukemia (CLL), you detect a mixture of relief and excitement. Keating, chief of clinical studies in the Department of Hematology and associate vice president for clinical investigation, remembers when the medical community almost dismissed fludarabine—initially used to treat acute leukemia—as too toxic. Phase I and II acute leukemia studies showed that high-dose fludarabine had a devastating side effect: severe nerve damage.

“The damage was so distressing that it almost stopped investigation of the drug,” Keating said.

Fortunately, other research on its use at lower doses in low-grade lymphoma and CLL saved fludarabine from investigational oblivion. In contrast to acute leukemia, these cancers could be treated with doses that were two- to fourfold lower, doses low enough to minimize general morbidity and eliminate nerve damage. The drug that was almost written off became a promising new agent for CLL treatment.

For the past several years, Keating, William Plunkett, Jr., Ph.D., and their clinical colleagues at The University of Texas M. D. Anderson Cancer Center have devoted much of their research efforts to fludarabine. A cure for CLL remains elusive, but the recently demonstrated effectiveness of fludarabine not only has expanded current treatment options but also has opened the door to the second tier of CLL research: determining a way to revitalize the immune system, which is incapacitated by CLL.

CLL—the most common form of leukemia in the Western world—grows slowly and occurs primarily in the elderly. These two factors, in addition to the lack of

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