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Clinical Cases

Clinical Trials and End-of-Life Decision Making

Physicians can help oncology patients decide whether to focus on aggressive chemotherapy or less aggressive comfort measures for end-of-life care.

Commentary by Dave Alberts, MD, and Lucy Godley, MD, PhD

Alice Wilson's daughter finally convinced her mother to make an appointment with the family physician 2 weeks after Alice's 65th birthday. Alice organized a garden party to celebrate, and it was a great success with all 5 children, 14 grandchildren, and most of her neighbors in attendance. Alice attributed her 20-pound weight loss and fatigue to the preparations for the party. She didn't tell anyone about the pain in her stomach that had been keeping her awake off-and-on for 6 months. It was only after the party—when she could no longer explain her fatigue—that Alice reluctantly agreed to see her physician.

Instead of a garden party, Alice spent her 66th birthday in the hospital recovering from her second surgery, this time to remove 3 suspicious lymph nodes and intra-abdominal metastases seeded from the advanced adenocarcinoma removed from her colon the previous summer. Since the first surgery, one of her children or her husband Will have been driving Alice for her weekly rounds of chemotherapy with Dr. Tseng, her oncologist. Almost a year later, he knows the names of all 5 children and most of the grandchildren, including the 2-week-old granddaughter named Alice .

Alice resumed her chemotherapy 3 weeks after the second surgery. At every visit she asks Dr. Tseng the same question: "What are my numbers, Doctor?" she wants to know. Immediately following the surgery Alice 's CEA levels dropped, and for a few weeks she would joke with the nurses who started her IV. "Careful with that," she would say, smiling, as one of them slipped a needle into the vein behind her elbow. Several months later the jokes stopped as her CEA values began to creep up again, gradually at first and then faster and faster.

At a special appointment between rounds of chemotherapy, Dr. Tseng tells Alice that the surgery and chemotherapy are slowing down the cancer growth, but they haven't been able to stop it. Alice doesn't say anything. She is tired all the time, she doesn't want to eat, the pain in her stomach still keeps her awake at night, and she has lost an additional 25 pounds. She has not yet been able to take baby Alice for a walk because she is too tired to push the stroller more than a few blocks. Dr. Tseng hesitates. Should he tell Alice about Zorvax, a new angiogenesis inhibitor in Phase II clinical trials? Clinically, Alice would be an ideal patient to enroll in the trial, and the latest publications about Zorvax indicate that many patients respond favorably. "There is something else we can try," he tells her, as he explains about the experimental medication. "This drug works in a different way than your current chemotherapy," he says. "It might be able to help slow down the cancer and give you more energy." Alice pauses for a moment. "I don't know," she says at last. "I don't know how much more chemotherapy I want to do. Will I still be so tired all of the time? I just don't know. What do you think I should do?"

Commentary 1

by David S. Alberts, MD

AW's clinical situation, unfortunately, is still commonplace in the management of stage IV colorectal cancer. There

are approximately 146,900 new cases of colorectal cancer each year in the United States and approximately two-thirds of these patients present with regional or distant disease [1]. Obviously, for both AW and the US population, this situation represents a sad public health failure, in that colorectal cancer is a preventable disease.

AW has undergone primary surgery, followed by adjuvant chemotherapy and secondary surgery, as a result of recurrent disease, which appears to be progressing intra-abdominally on the basis of a rapidly rising serum CEA. She has lost at least 20 to 25 percent of her body weight, has become weak, experiences moderately severe abdominal pain, and clearly has had a major reduction in her clinically determined performance status. Her medical oncologist has developed a close relationship with AW and her family and is being asked critically important questions related to end-of-life care.

There are several important issues to discuss concerning the current and future management of the more than 56,000 patients who will die from colorectal cancer each year. First, let us examine the role for secondary or tertiary chemotherapy of progressive, recurrent, metastatic colorectal cancer. Recently, 2 molecularly targeted agents, bevacizumab (VEGF inhibitor) and cetuximab (EGFR inhibitor) and 1 new cytotoxic agent, oxaliplatin, have been approved by the FDA to treat newly diagnosed or recurrent metastatic disease [2-4]. Responses to these agents either as first- or second-line single agents or in combination with 5-fluorouracil plus leucovorin or irinotecan are in the range of 10 to 50 percent with survival prolongation of perhaps 2 to 4 months. However, the population of patients treated in the phase III clinical trials establishing the activity of these 3 new drugs likely all had a better performance status than does AW. This is important, because response rates and survival durations are highly correlated with performance status. AW's weight loss and severe weakness generally translate to a poor performance status category (ie, performance status grade 2/3 on the Southwest Oncology Group scale) [5]. In fact, such an excessive weight loss (ie, 45 lbs) is associated with negative nitrogen balance and significantly compromised immune function, all of which predict lack of response to either cytotoxic or molecularly targeted agents. Most early phase clinical trials of new cytotoxic or biologic drugs require a patient performance status of at least 2 (ie, moderately symptomatic, but not requiring physical assistance) and, commonly, 0-1 (ie, either a totally asymptomatic patient or one whose symptomatology does not impair function). Thus, it is unlikely that AW would qualify for a clinical trial of the new agent, Zorvax, as discussed in the case report.

Does this mean that there is no treatment or hope for AW? The answer is a resounding "no." There is treatment for this very deserving woman who wants to spend quality time with her family at this point in her disease process. Any board-certified medical oncologist should have received training in end-of-life management that included knowledge of therapeutic modalities for pain management, prevention of nausea and emesis, anorexia control, and management of severe constipation. Modern therapeutics requires intensive intervention in the end-of-life situation, and no form of cytotoxic agent or biological therapy can be successful without adequate supportive care. Finally, considerable effort is being directed toward understanding the cachexia syndrome, clearly affecting the quality of AW's life [5]. With the identification of cachetic factors, it will be possible to develop a rational approach to therapeutics for this devastating condition.

Should Dr. Tseng put AW on a clinical trial, if she qualifies for enrollment? Obviously, the most important person to answer that question is AW. Given direct and honest answers to her questions, it is highly likely that AW would choose best supportive care for her end-of-life management. All too often, the medical oncologist replaces excellent supportive care with a cytotoxic or biologic agent that may have virtually no chance for producing tumor response or improved quality of life. The choice to pursue further drug therapy also replaces vitally important, direct and honest patient-physician communication. Unfortunately, this critically important aspect of clinical oncology is still inadequate in our post-doctoral fellowship training programs.

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Commentary 2

by Lucy Godley, MD, PhD

This case illustrates a common situation in the treatment of cancer patients—deciding when to continue therapy aimed at disease control and when to initiate measures designed to maximize patient comfort. In this example, the patient is a 66-year-old woman who has been treated aggressively with multiple surgeries and numerous chemotherapy regimens for advanced-stage colon cancer. This is a realistic scenario, since there are many active chemotherapy agents available for colon cancer and several different ways to combine them. The patient, now tired, worn out, and in pain, asks her doctor whether she should continue therapy directed at controlling her disease.

Chemotherapy treatment today is much better tolerated than in years past, thanks to numerous agents that support cancer patients [1]. Several growth factors are available that stimulate white blood cell production by the bone marrow (G-CSF and GM-CSF), thus allowing chemotherapy regimens to be given with high intensity and on accelerated schedules with improved efficacy [2]. Chemotherapy-induced anemia can be treated with erythropoietin and its derivatives, which stimulate red blood cell production, alleviate the tiredness associated with prolonged chemotherapy, and augment chemotherapy and radiation effectiveness [3]. Several new and highly effective agents are available to treat chemotherapy-induced nausea and vomiting, making chemotherapy much more tolerable [4]. Cannabinoids can stimulate the appetite as well as control nausea and vomiting. Many narcotic and non-narcotic analgesic agents are available to treat cancer-associated pain. For example, radiation can often be used to palliate the pain associated with bony metastases. In the case at hand, one wonders whether Mrs. Wilson's symptoms of tiredness, anorexia, and pain have been adequately addressed. She has been seeing her oncologist weekly for some time, so there should have been ample opportunity to discuss these issues. Oncologists should aggressively manage the symptoms associated with cancer therapy in the interests of improving quality of life for patients.

When oncologists are faced with questions like Mrs. Wilson's—should she try an experimental therapy or just accept palliative care—they must use careful judgment in answering. Since physicians in private practice receive direct financial payment based on the administration of chemotherapy, oncologists must conscientiously separate clinical assessment of the patient from the financial needs of their practices, and they must be clear with themselves and their patients that patient welfare—not personal interest—is their primary concern. Physicians in academic centers may feel less of a direct financial reward from treating patients. Nonetheless, all physicians must ask themselves when treating relapsed patients, "When should we change the focus of care from one of controlling the disease to one of comforting the symptoms?"

Patients whose disease progresses after they have received standard treatment regimens often become candidates for

investigational agents. Drugs in Phase I testing are being studied for toxicity in humans, while drugs in Phase II testing are being studied for efficacy. The decision to enter into a clinical trial must be preceded by full disclosure to the patient as to the purposes of the study. Patients should be given written consent forms to read and discuss before entering into the study. They should have realistic expectations as to what outcomes they seek to gain from the trial. Achieving this can be difficult with patients who are in denial about their disease and its prognosis, but physicians must be forthright and persistent about realistic expectations.

Hospice and programs with similar goals accept patients with an approximate life expectancy of 6 months to 1 year [5]. Unfortunately, oncologists are notorious for referring patients to such programs when they have only a few days or hours to live. Such late referrals do not allow patients or family members to experience the benefit of the superb care provided by these programs. Comfort-care approaches should not be seen as "giving up" on a patient but as active management of patients. Physicians and nurses should help patients accept that they are at the end of their lives and that the focus of care will now shift to controlling their symptoms instead of the primary disease process.

Each patient is unique and has his or her own style of decision making. Physicians should try to incorporate patient and family goals into each decision. In this case, when Mrs. Wilson asks, "What do you think I should do?" Dr. Tseng can be most helpful by redirecting the question to her and saying, "Well, that depends on what your goals are at this point." The doctor, patient, and family members can then discuss expectations of further chemotherapy versus comfort-level approaches. If Mrs. Wilson wants to do everything medically possible to treat her disease, then she might decide to continue on with a Phase I or II study. If, however, she feels that she is getting incrementally less and less benefit with each treatment and would prefer staying home and maximizing her comfort at this time, she might choose to stop chemotherapy and enter a hospice program.

The most appropriate and informed decision will result from open, candid discussion among the patient, her family, and her doctor, after realistic expectations have been outlined. Once engaged in such a conversation, Mrs. Wilson may again ask Dr. Tseng what he thinks she should do. At that point, Dr. Tseng may feel comfortable expressing his opinion directly. If Mrs. Wilson were my patient, I would speak with her and her family and encourage her to consider entering a hospice-type program.

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