Is It Time to Inform This Patient that Further Antineoplastic Drug Therapy Will Not Be of Clinical Value?

Maurie Markman
University of Texas M.D. Anderson Cancer Center, Houston, Tex., USA

Key Words
Advanced cancer · Antineoplastic drug treatment · Cost · Cost-effectiveness · Medical futility · Patient’s right to decide · Toxicity

Abstract
A woman with heavy pre-treated ovarian cancer sought consultation regarding additional treatments. The case raises the vexing question of whether there may be a time in the course of the disease process where it is most appropriate to state further anti-neoplastic therapy will not be of clinical utility.

Background
There have been complex discussions recently in both the medical literature and the lay press regarding the relative value and clinical utility of new, and often quite novel, pharmaceutical agents employed as treatment of advanced cancers. It is reasonable to acknowledge that much of this debate has focused on the critically important issue of the relative cost-effectiveness of such therapies, whether that cost is to be borne by a governmental agency, an employer, a third-party insurer, or the individual patient/family [1].

Further, there is also the question of the potential toxicity of such treatments, particularly in the setting of older cancer patients with pre-existing co-morbid medical conditions (e.g. past history of a myocardial infarction, diabetic renal dysfunction, etc.). Here the issue is the valid concern that any theoretical potential for benefit must be weighed against the probability the therapy may produce harm.

Less often heard in these debates is perhaps an even more vexing question, that of the fundamental right of cancer patients to decide that they want to initiate or continue therapy, independent of the fact an objective external observer reviewing the situation...
may declare that based on existing evidence of potential benefit such a decision must be considered to be extremely unwise or outright irrational. Assuming the cost of additional therapy is not a determining factor (e.g. the family will pay), and the risk of serious toxicity is not an overwhelming concern, should patients be permitted to simply declare they wish to receive a specific treatment that may be available for their condition? Or does a physician have an obligation in certain circumstances to state that further antineoplastic drug treatment should not continue due to the absence of a realistic potential for any clinical benefit?

A requested consultation involving a heavily pre-treated ovarian cancer patient represents a poignant example of this ethical dilemma.

**Case Report**

A 43-year-old female presented with ascites and was found to have a malignancy (papillary adenocarcinoma) diffusely involving the peritoneal cavity. The serum CA-125 antigen level was 8,000 IU/l. The patient experienced an excellent initial response to primary platinum-based chemotherapy (2 cycles of cisplatin/cyclophosphamide followed by 6 cycles of carboplatin/paclitaxel) with a decline in the CA-125 antigen level to 148 IU/l. Treatment was continued with 4 cycles of a carboplatin/gemcitabine regimen, but the tumor marker increased to 400 IU/l. At this point in time radiographic imaging of the peritoneal cavity revealed no tumor masses.

However, following 2 additional cycles of carboplatin/cyclophosphamide the CA-125 had increased to >1,000 IU/l, ascites returned, and there was evidence of macroscopic disease within the peritoneal cavity. The patient was treated with a program of pelvic radiation and concurrent weekly docetaxel plus bevacizumab. There was a modest decline in the CA-125 antigen level (<50%) and ascites appeared to decrease somewhat. Treatment was continued with carboplatin, docetaxel and bevacizumab. Following a slight increase in the CA-125 antigen level, treatment was changed to cisplatin, topotecan and bevacizumab, and subsequently to oxaliplatin, irinotecan and bevacizumab. At the time of clinical progression a laparoscopy was performed which revealed diffuse small implants (each <1 cm in maximum diameter) throughout the peritoneal cavity. The patient was subsequently treated with liposomal doxorubicin and then with a program of paclitaxel and vinorelbine. Unfortunately, there was further evidence of disease progression on this most recent regimen.

However, the patient maintained a good performance status, was essentially asymptomatic at the time of the consultation, and strongly desired additional treatment.

**Discussion**

At the time of the request for input into possible future therapeutic options, this patient had already received 10 chemotherapy regimens that included a total of 11 different antineoplastic agents. She had also undergone pelvic radiation. While her overall clinical condition was fortunately quite reasonable, and there were no specific medical contraindications to continuing chemotherapy, this case raises the possibly uncomfortable question that perhaps the issue to be addressed in this situation was not ‘what drug to give next’, but rather whether it was appropriate that any additional antineoplastic agents should be administered.

As a recent commentary written by physicians in a medical intensive care unit who were caring for an elderly woman with advanced multiple myeloma eloquently describes [2], it can be very difficult for some patients with progressive malignancies (and their families) to accept the concept of withholding further management strategies directed at treating the cancer, as this decision clearly implies the acceptance that the cancer will result in the death of the patient. By continuing to focus ones energies on ‘fighting the
cancer’, some individuals appear to be able to delay the consideration of what are apparently unacceptably distressing thoughts and feelings.

Unfortunately, the end result of this avoidance may be side effects, whether relatively minor or more severe, and the very real potential for a more rapid deterioration in overall quality of life than would have occurred in the absence of treatment strategies that have no realistic chance of producing a favorable impact on the future course of the illness. Avoidance of what is emotionally and psychologically difficult may lead, even if completely inadvertent, to serious harm.

It is important to acknowledge that not all treatments considered for administration in individuals with similar characteristics to those described in this case report will result in major side effects (e.g. cisplatin-induced neuropathy/hearing loss, etoposide-associated secondary acute leukemia). However, even more modest toxicities (e.g. mild nausea, moderate fatigue) may negatively influence a patient’s activities of daily living and the enjoyment of her/his remaining time with family and friends.

An additional component of this discussion is the complex and controversial issue of medical futility. It is generally accepted that physicians are not ethically required to offer, or participate in, care that is medically futile, even if requested or demanded by patients and/or their families [3–5]. In this context, ‘medically futile care’ usually refers to the complete absence of evidence a particular intervention can achieve the desired physiologic effects (e.g. a procedure designed to restore heart function following a prolonged cardiac arrest), rather than the absence of a reasonable chance the specified intervention will improve quality of life or extend survival.

It is appropriate, in fact mandatory, to declare that individual physicians should never be permitted to ‘play God’ and substitute their personal value systems regarding the utility of medical procedures or anti-cancer therapies [6].

However, it can similarly be suggested that based on carefully considered objective data, the oncology community (perhaps represented by internationally recognized and respected cancer organizations), with strong input from nonmedical sources (e.g. patient advocates, biomedical ethicists, governmental/regulatory officials, members of the clergy), can develop rational statements regarding what may be considered in specific circumstances to be medically futile therapy when delivered to directly impact the clinical course of the cancer. Under such circumstances, when an expressed desire for more treatment is beyond the realm of a rational decision, one can legitimately argue that further therapy is not medically indicated and need not be provided.

It is critical to acknowledge here that this discussion has nothing to do with the delivery of known effective therapies designed to palliate specific (e.g. external beam radiation directed to a painful pelvic sidewall mass) or more general malignancy-associated symptoms (e.g. narcotic analgesia for pain control).

Clearly, the decision by patients to continue or stop antineoplastic drug therapy is extremely complex, emotionally laden, and not formula driven. While it is not possible to provide a simple roadmap for oncologists as to when they need to definitively declare, or at least strongly state, that further treatment directed toward shrinking the tumor or preventing an established pattern of progression is futile, it is also reasonable to conclude that in certain settings this is a role a caring and compassionate physician must consider assuming.
References

1. Warren JL, Yabroff KR, Meekins A, Topor M, Lamont EB, Brown ML: Evaluation of trends in the cost of initial cancer treatment. J Natl Cancer Inst 2008;100:888–897.

2. Drazen JM, Desai NR, Green P: Fighting on. N Engl J Med 2009;360:444–445.

3. Schneiderman LJ, Jecker NS, Jonsen AR: Medical futility: its meaning and ethical implications. Ann Intern Med 1990;112:949–954.

4. Cantor MD, Braddock CH III, Derse AR, Edwards DM, Logue GL, Nelson W, Prudhomme AM, Pearlman RA, Reagan JE, Wlody GS, Fox E: Do-not-resuscitate orders and medical futility. Arch Intern Med 2003;163:2689–2694.

5. Committee on Ethics, American College of Obstetricians and Gynecologists: ACOG Committee Opinion No. 362: Medical Futility. Obstet Gynecol 2007;109:791–794.

6. Curlin FA, Lawrence RE, Chin MH, Lantos JD: Religion, conscience, and controversial clinical practices. N Engl J Med 2007;356:593–600.