The Kenneth B. Schwartz Center Rounds

A Staff Dialogue on Phase I Trials: Psychosocial Issues Faced by Patients, Their Families, and Caregivers

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Key Words. Cancer · Phase I clinical trials · Informed consent · Caregivers · Psychosocial · Palliative care

ABSTRACT

Shortly before his death in 1995, Kenneth B. Schwartz, a cancer patient at Massachusetts General Hospital, founded The Kenneth B. Schwartz Center to be housed at Massachusetts General Hospital (MGH). He created this center to advance the hopes, goals, and ideas expressed in his article, “A Patient’s Story,” published in the July 16, 1995 issue of the Boston Globe Magazine. The Schwartz Center is a non-profit organization dedicated to strengthening the relationship between patients and caregivers and to supporting and advancing “compassionate health care delivery in which caregivers, patients and their families relate meaningfully to one another in a way that provides hope to the patient, support to caregivers and sustenance to the healing process.” One of the Center’s major projects is the sponsoring of the Schwartz Center Rounds, a monthly, multidisciplinary forum in which caregivers discuss a specific cancer patient and the important psychosocial issues faced by the patient, family and caregivers. The forum allows caregivers to reflect on their experiences with patients and to gain support and insight from fellow staff members.

The following case discussion was addressed at the January 1998 Schwartz Center Rounds. In this article, the case will be presented, followed by verbatim dialogue from the rounds and a subsequent discussion of the relevant issues with emphasis on staff psychosocial issues.

J.T. was a 43-year-old man who developed adenocarcinoma of the lung and was treated at MGH. He died while participating in a phase I trial, resulting in marked frustration and distress among his caregivers. Staff questioned whether cancer patients entering phase I trials and their families receive unbiased information about the possible risks and benefits of the trial. They were also concerned about whether or not patients and their families really understand the physical and emotional risks of a trial. Moreover, they addressed whether patients are presented with alternatives to enrolling in a phase I trial, such as palliative care. Despite all these concerns, caregivers are reconciled to the belief that patients do value the opportunity to participate in phase I trials, in that they can contribute hope and meaning to other patients’ struggles with cancer. The Oncologist 1998;3:357-364

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The Oncologist 1998;3:357-364
PRESENTATION OF CASE

This case was discussed at the Schwartz Center Rounds at Massachusetts General Hospital in January of 1998. The Schwartz Center Rounds is a monthly multidisciplinary forum in which caregivers discuss a specific patient with cancer and the important psychosocial issues faced by the patient, family, and caregivers.

In June of 1995, a 43-year-old previously healthy man, J.T., presented to the Massachusetts General Hospital with a short history of a nonproductive cough and in an otherwise good state of health. He was a non-smoker, and his past medical history was unremarkable.

A chest x-ray revealed a lobular 5.0 × 3.0 cm right hilar mass. A bronchoscopy, mediastinoscopy, video thoracoscopy, and wedge resection were performed, confirming the diagnosis of adenocarcinoma of the lung. Thoracoscopy revealed diffuse metastases to the pleura, rendering the tumor unresectable. CT scan showed metastatic disease with two right upper lobe lung nodules and two brain metastases. Cranial irradiation was targeted at his brain metastases, which subsequently remained radiologically and clinically stable. Despite his diagnosis and initial irradiation, J.T. continued to work full time.

J.T. worked for a local utility company. He was an active and optimistic man with a strong will to survive. He had a wonderful sense of humor and was always upbeat. J.T. was extremely devoted to both his career and his family. He had been married for over twenty years to his high school sweetheart and had two teenage sons, one of whom graduated from high school and went on to college during J.T.’s illness. J.T.’s family and friends were extremely supportive of him throughout his battle with cancer. J.T.'s sister, involved in health care research, as well as his wife, were very involved in both his health care and his treatment decisions.

During the next two and a half years, J.T. was treated with multiple courses of chemotherapy, including carboplatin and Taxol, 9-amino-20[F]-camptothecin, cisplatin and gemcitabine, and Navelbine. Later in his disease course, he also received radiation therapy to his lung. Despite all of these approaches, his metastatic lung cancer continued to slowly progress with multiple lung nodules. His pulmonary function worsened, and he became short of breath. Nevertheless, J.T. maintained a positive attitude and continued to work part time.

In November of 1997, he chose to participate in a phase I gene therapy study. In January 1998, as a part of the study, a left video-assisted thoracic surgery, pleural biopsy, and excision of a right supraclavicular lymph node were performed to harvest tumor for a tumor vaccine. Initially, J.T. tolerated these procedures well. However, postoperatively his respiratory status rapidly deteriorated, and he became unresponsive. He was emergently intubated and transferred to the Intensive Care Unit for ventilatory support. J.T. self-extubated himself twice, and his condition progressively deteriorated despite treatment with broad-spectrum antibiotics for pneumonia.

J.T. had neither an advanced directive nor a DNR status. After extensive discussions with his family, they decided to discontinue his ventilatory support and provide him with comfort measures. On January 23, 1998, J.T. died from respiratory failure, with his family present at his side. His death was recorded as an adverse event of the protocol, although it was more than likely a result of his advanced cancer.

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DIALOGUE

Doctor: If we are going to change the outlook for patients with cancer, then we need to be at the forefront of testing new drugs, new ideas, and new therapies. Some of these clinical experiments are dangerous, and some of them have serious toxicities and side effects. So the whole idea of creating a center for drug evaluation at MGH carries with it a new set of problems for the nurses and the staff.

The Decision to Accept Phase I Treatment

Nurse (who presented the case): Because he had tolerated all of the multitudes of previous treatments so well, he and his wife had never really been put in a position of having to even consider the notion of a DNR status. His wife told me a couple of weeks ago that they had never even discussed his end-of-life wishes at home.
J.T. was incredibly positive and would never have allowed any discussion of the potential of his cancer to get the better of him. Considering the length of time he survived with such advanced disease, he did remarkably well, perhaps due to his optimism. It made it very difficult for his wife because she was now faced with the decision of having to take him off the ventilator, allowing him to die. I credit his doctor for helping her realize that a decision did not really need to be made. It was already made. He could not live this way.

I think the hardest thing for me, when I went to see the family after he passed away, was that his two sons were very angry, partly because they had just lost their father, but more so because they felt that they did not have an opportunity to say good-bye. They did not fully realize or understand when he went in for this procedure what the risks were. I am sure that they were told, but people tend to hear what they want to hear. J.T. was loaded with tumors, and he probably would not have lived that much longer, probably weeks, maybe months if he was lucky, had he not undergone this procedure. Nevertheless, his children never had an opportunity for closure.

Doctor: A similar event, death due to adverse consequences of an experimental procedure, could be described as a direct result of an experimental drug. The incidence of fatal complications with phase I drugs is high. Most people think that the issue is whether the drug “might or might not work” and that the chances of it working are maybe 2%, 3%, or 5%. But the reality is that phase I trials are conducted by escalating the dose or undertaking a new procedure until an intolerable toxicity is reached, at which point some patients do die. Often this reality is not really clear to a patient when they start a study.

The Nurse’s Dilemma

Nurse: The hardest thing about treating a patient on a phase I trial is trying to balance quality of life and quantity of life. Phase I trials were all phase I drugs at some point. So I know that these trials need to be done. But it is still hard.

Doctor: I think sometimes caregivers do their patients a disservice by promoting phase I trials because often supportive care and hospice care are not presented as viable options. Sometimes patients on phase I protocols get so sick that it accelerates the process. The gene study that J.T. was enrolled in had minimal side effects, but I have given other phase I drugs to patients to whom I have wanted to say, “Anytime you want to quit, you can.” I realize it is a horrible thing to say, because what kind of message does that send to your patient? But one particular study made patients deathly ill. They were miserable. Their discomfort was the worst I have ever seen, and it pained me to be the one giving them the drug. As a nurse, I am supposed to help patients with “end-of-life issues” and help them feel better, but I find myself in a situation making them feel worse. Yet I know that present standard care chemotherapy drugs were all phase I drugs at some point. So I know that these trials need to be done. But it is still hard.

Doctor: For patients, it is a “trade-off” between the uncertainty of whether the drug will work and the certainty that if we cannot find something that is going to work, they are going to die. It is a huge gamble for the patient, but ultimately it is their decision whether or not to take the risk.

Do doctors adequately present the alternatives of ceasing aggressive therapy or providing palliative care? We are a pretty activist group of people here. We test our drugs, and we have this optimism that everything is going to work. But are our patients fully informed of other treatment options?

Doctor: I think the physicians who present phase I trials to patients are all incredibly biased. Many times the physicians are the principal investigators in the trial themselves. Often they are inappropriately optimistic or enthusiastic about the trial they just spent 100 hours designing. One study suggested that patients...
believe that their chance of responding to a phase I trial is about 50%, when the reality is really about 1%-2% [1]. My guess is that the doctor probably did not say 50%, but he probably said something like, “This is new; we don’t really know.” “It’s like a coin flip,” or “Who knows; it either will or it won’t work.” These types of statements probably get misinterpreted as a 50-50 chance.

**Doctor:** If to feel better and to live longer are the reasons patients go on a trial, it is very likely that most patients who go on phase I studies probably would have felt better and lived just as long with palliative care. But they would not have any hope of getting better.

**Nurse:** But is it false hope?

**Doctor:** It is not false hope, because there are select patients who do benefit from phase I trials. It is not a 1% or 2% response rate for every drug. Some drugs work and others do not. Some lucky patients happen to go on a cisplatinum or a Taxol as their therapy, and a substantial number of them benefit from it. But then there are many drugs from which no one benefits.

**Palliative Care as an Alternative**

**Palliative Care Specialist:** Every patient should be offered the best alternatives to their therapy. Palliative care is the best alternative to doing nothing, and it is the prime alternative to the phase I trial. My main concern is that I am not present when decisions to go on a phase I trial are made. Certainly, it is important that a patient is fully informed before he or she decides whether to opt for palliative care or a phase I trial. Patients should be aware that at any point, palliative care is always an option for them.

**Doctor:** Do you think that as standard procedure we ought to require that all our phase I candidates have a palliative care consult so they can get a clear picture of the alternative?

**Palliative Care Specialist:** Yes, I do. It is a very difficult situation when caregivers do not have anything promising to offer a patient. A patient should never be offered nothing. They should be presented with their options. One option is to make the best of one’s time, to be in control, and to get supportive care.

**Closure**

**Nurse:** One disturbing aspect about this case is that his family never had a chance to have closure. I knew J.T. well, and I know how hard it was on him and his family. I treated him many times, and we could not talk to him about end-of-life issues. He just would not let you. It makes me really sad because as caregivers we feel like we did not do our part to help the patient and the family to do the right thing in the end. I think we end up being resented some of the time. When we talk to patients, how we say things and how they let us say things to them determine how and what they hear from us. I think we feel a lot of responsibility when things do not go right for people. But a lot of times they dictate that to us, and it is hard to know what else we could have done. You ask yourself, “Could I have done something more?”

**Doctor:** Do you think that the patient’s family had a clear appreciation that he was so close to the end?

**Nurse:** From what I have seen, older patients tend to have more of a gradual decline. They become more debilitated from their treatment so it is not usually a huge surprise when they die. I have treated quite a few patients in their thirties who look great and seem to be doing well but who show evidence of very advanced disease on their scans. They are leading productive lives with minimal symptoms, and it is hard to believe that this scan belongs to that person. So, in these sorts of cases, I do not think the family fully comprehends the severity of the situation.

**Doctor:** Are patients’ children fully aware of the severity of the disease and the risks of a phase I trial when treatment is initiated?

**Nurse:** They are usually told, but I do not think that they really get it internally. Kids are often the last ones to know. In this case they did not know. Suddenly, their father was just gone.

**Doctor:** There are usually two scenarios. If a patient really wants to participate in a clinical trial, the family
will almost never dissuade them. On the other hand, I have seen family members push loved ones onto clinical trials. Often the patient will say, “Oh, I’m tired,” and the spouse will say, “Oh no, no, you feel fine. You have plenty of energy. Tell me, doctor, let’s hear a little more about this clinical trial...Oh, that sounds very interesting. We think...”

**Doctor:** Maybe before we put patients on a trial we ought to ask them: “Do your family members know that you are going on this trial? Are they comfortable with it? Do they understand the consequences?” We tend to focus on patients and patient autonomy. We made the transition from doing trials without informed consent to being sure that we ask patients if they want to be on the trial, but we do not really conscientiously ask that question of the family. In some cases, families are actively involved, but in others they are uninformed and unaware of the trial and its possible consequences.

I do not know if family members are being told or fully understand that it is a trial, an experiment. They do not realize that it might not work, and that in fact it probably will not work, and that it could even kill their loved one. Often, they do not fully comprehend the “uncertainty” of it all. Everybody is in a rush to get things done, so those messages often do not sink in. Also, I think patients are rarely told or rarely hear, “You don’t have to do this. There are other things that can be done to help you in the last stage of your disease.”

**Nurse:** The patients need to be given time to think about what they are faced with. When they are first introduced to a phase I study, patients are really dealing, maybe for the first time, with their own mortality, and that takes up a lot of emotional energy. It is not until later that they can really think clearly about what they are faced with and make an informed, rational decision. I do not think we should rush anybody onto a phase I trial.

**Doctor:** Is it right to feel comfortable about enrolling patients in phase I trials? It seems to me it is an area of clinical research that we are never really going to feel comfortable about. The tremendous odds against the patient responding and the fact that, in the end, patients are basically sacrificing for the sake of science and for others make caring for patients on phase I trials very uncomfortable. It is difficult because we, as caregivers, know that most of these people are not going to be helped and that there are serious life-threatening risks involved.

**Nurse:** But certainly, if we feel that our patients truly understand the nature of a trial, our “comfort level” will be much greater because we will know that they are fully informed, that they are seeing it clearly and not as some “magic bullet.”

**Social Worker:** Most patients tell me they feel like they do not have a choice, especially if palliative care is their only other option. They are choosing life, or what they think is going to mean life for them, prolonged life, extended life. Patients often “push on” regardless of how many times they are told that the chances of the trial helping them are minimal.

**DISCUSSION**

This dialogue among caregivers, concerning a patient who died as an adverse event of a phase I clinical trial, raises many important ethical and psychosocial issues pertaining to late-stage treatment options for terminally ill cancer patients. The overriding sentiment that emerged from this conversation was the staff's discomfort with treating patients on phase I trials. This case was particularly provocative of such emotions because J.T. died as a direct result of a clinical trial. Several major questions concerning phase I trials arose from this dialogue:

▲ Do staff offer patients and their families unbiased information about the possible risks and benefits of phase I trials?

▲ Do patients and their families really understand the physical and emotional risks of a phase I trial?

▲ When presenting the option of a phase I trial to a patient, do caregivers present other alternatives to their patients, such as palliative care?

**Phase I Trials**

Phase I studies, which define dose-limiting toxicities and the maximum tolerated dose of new drugs prior to evaluation of their efficacy in phase II trials, evoke many ethical issues that confound the testing of these new therapies. These competing moral considerations can make staff uneasy about treating patients on these trials.

The possibility of beneficial response to phase I treatment is quite small. In a collection of phase I trials published from 1972 to 1987 [2], Decoster reported that 0.3% of cancer patients on phase I trials responded completely to the experimental agent, while 4.2% responded partially. Toxic deaths were reported in 0.5% of the population. Despite the low response rate, the authors speculated that some therapeutic benefit can be achieved from phase I trials. However, the fact that more people die from phase I trials (0.5%) than experience a complete response (0.3%) raises ethical issues that compete with the scientific necessity of performing these trials. Are caregivers, patients, and their families really cognizant of these odds?
Do Staff Offer Patients Unbiased Information About Phase I Trials?

In this discussion, staff expressed discomfort in treating J.T. because they did not feel that he and his family had a realistic understanding of the small benefit and high risk that phase I trials offer.

Legally, the amount of information regarding diagnosis and prognosis that patients receive is a highly contentious issue. In a groundbreaking report in 1961, Oken found that 90% of 219 physicians surveyed (internists, obstetrician-gynecologists, and surgeons) did not tell patients about a diagnosis of cancer [3]. However, a follow-up study in 1979 found that 97% of physicians indicated a preference for disclosing the diagnosis [4]. While studies have found that at least one-third of patients prefer to leave decision-making to the doctor alone [5], and that physicians do filter what they believe their patients do not want to hear [6], it is now universally accepted that patients have the right to be fully informed about their diagnosis and proposed treatment [7, 8]. If competent and rational, patients have the right to make their own treatment decisions or to have a legal surrogate appointed [7-9]. In clinical trials, the minimal safeguards for the patient need to remain IRB approval of the study and informed consent by the patient or his or her legal surrogate.

As staff expressed in this dialogue, ensuring that patients are offered full information about trials is crucial, not only to maintain respect for patient autonomy, but also to enable caregivers to feel comfortable administering experimental treatments.

Do Patients Clearly Understand the Physical and Emotional Risks of a Phase I Trial?

While patients may be offered verbally and in writing full information about the risks of phase I trials, often this information is filtered by patients, as observed by the staff in this case. Often patients do not fully comprehend the purpose of a phase I trial. In a study conducted by Daugherty, 93% of patients participating in a phase I trial said they understood all (33%) or most (60%) of the information provided about the trials in which they had chosen to participate. Yet when asked an open-ended question about the purpose of a phase I study, only 33% of participating patients understood that its main intent was to determine maximal dose and tolerability of the drug. More than half (52%) erroneously believed that the main goal of the study was to determine response and therapeutic benefit [1, 10].

Studies have shown that this misinterpretation of the purpose of phase I trials can lead to unrealistic hopes of patients on these trials [1, 10, 11]. Patients are often willing to endure painful and inconvenient treatments if there is the slightest chance of a cure. An influential study investigating patients’ attitudes toward chemotherapy found that 53% of patients would accept aggressive treatment with serious side effects with only a 1% chance of cure, whereas only 13.5% of cancer nurses and 20% of oncologists would accept aggressive treatment with the same odds [12].

A recent analysis of the SUPPORT study [13] reported that patients who thought that they were going to live for at least six months were more likely (OR = 2.6; CI = 1.8-3.7) to favor life-extending therapy over comfort care, as opposed to patients who thought that there was at least a 10% chance that they would not live six months. Patients vastly overestimated their chances of surviving six months, while physicians estimated quite accurately. While phase I trials are pharmacological experiments necessary to advance medical treatments, this goal can conflict with the hope that patients derive from such studies, creating an uncomfortable and perhaps unresolvable tension for caregivers.

Because of their stressful situation, cancer patients have an understandable tendency to interpret information positively. This discrepancy between what patients are told and what they internalize causes significant concern for caregivers and creates an emotionally charged and distressing responsibility for the staff.

Do Staff Offer Patients’ Family Members Unbiased Information About Phase I Trials and Their Likely Benefits and Risks?

While patients are for the most part informed about phase I trials and their risks, regardless of how they may interpret them, often family members are not. During the rounds, several caregivers expressed disappointment in J.T.’s children’s inability to have closure. Family members are an essential source of support for cancer patients [11, 14, 15], and while patient autonomy is of foremost concern in treatment decisions, perhaps family members, particularly children, should be more informed regarding phase I trials and their risks. Being informed allows family members to better prepare psychologically and emotionally for unexpected complications and for the death of their loved one.
When Presenting the Option of a Phase I Trial to a Patient, Do Caregivers Present Other Alternatives to Their Patients, Such as Palliative Care?

During the Schwartz Center Rounds, staff advocated for a more systemic presentation of palliative care as an alternative or an addition to a phase I trial. Caregivers felt uneasy that some patients may feel pressured to participate in a trial and may not be aware of the scope of palliation as an alternative. Because some physicians are so focused on testing new treatments and are reluctant to admit that aggressive treatment has ceased to be helpful, palliative care may be disregarded as an option or may be presented in a cursory manner.

There is evidence that palliative care, without anticancer treatment, is infrequently presented as a valid option to patients considering phase I trials. In one study on perceptions of cancer patients involved in phase I trials and their physicians, only 30% reported being offered no treatment or palliative care as an alternative [1]. Often statements in consent forms fail to reflect adequately alternatives to participation in a randomized clinical trial [16].

How a phase I trial is presented to patients can have profound influence on the treatment they choose and how they spend their last days. Since people assign different value to duration of life, symptom control, and performance status, patients should be afforded the opportunity to make informed decisions about their end-of-life treatments, weighing all possible options. The consensus of the Rounds found that all patients should be afforded palliation, symptom control, and psychosocial support regardless of whether they are on a phase I trial.

CONCLUSION

While phase I trials and the conflicting issues surrounding them may, at times, be distressing to staff, patients clearly do value the opportunity to participate in these high-risk studies [1, 10, 17, 18]. At the University of Chicago Medical Center, a Professor of English who was diagnosed with terminal cancer eloquently advocated for the involvement of patients in cancer research as a source of hope [19]. Wanting his death to contribute to the fight against cancer, he likened his participation in a phase I trial to a fallen soldier’s body with an identity tag. Although most patients are less altruistic, cancer patients appear to see themselves more as volunteers than victims, and the evidence appears to suggest that individual patients do benefit from and are enthusiastic about their involvement in clinical trials [20]. If cancer patients and their families are well informed about and understand the risks and benefits of phase I trials and are aware of other treatment options, phase I trials can provide great meaning to a patient’s struggle with cancer.

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**REFERENCES**


**Additional Reading**


