Explaining Marginal Benefits to Patients, When "Marginal" Means Additional but Not Necessarily Small

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Abstract

Patients and their families want us to be realistic, honest, and caring about their prognosis and their options, even when the news is bad. Most oncologists will tell a patient if he is not curable, but not give specific survival information unless prompted. As an example, chemotherapy for pancreas cancer improves survival and does not worsen quality of life, but the impact on lifespan is small. Patients with advanced pancreas cancer have options that increase their average survival by about 16/100 at 1 year, and by about 9 weeks compared with best supportive care, but almost all patients are dead by 24 months. As an example of "marginal benefit" ("marginal" is defined here as more than that offered by the alternative care, not necessarily small or worthless), erlotinib added to gemcitabine compared with gemcitabine alone improves survival by six additional people at 1 year, and an average of 2 weeks, with no survival tail. In addition, the additional drug cost alone can be more than $12,000 a month. We use this clinical practice as a way to describe marginal benefit to patients. Telling patients that they have incurable disease and that treatment is ineffective is hard. Partly as a result, only about a third of cancer patients are told they are going to die, and those who are not told live no longer but have worse medical outcomes, such as dying on a ventilator and less time with hospice. These difficult conversations can be done if the oncologist has the right medical information, the right script, and some decision aids. Clin Cancer Res; 16(24); 5981–6. ©2010 AACR.

The majority of medical oncology work is the treatment of people with metastatic disease. Curable illnesses such as lymphomas and testicular cancer represent a small percentage of the daily patient load seen in the typical medical oncology office. There has been an increase in patients receiving adjuvant treatment, but the majority of our work is dealing with people who have, at some point, a life-ending illness and who face increasingly small benefits from noncurative chemotherapy. Our patients tell us that they want us to be honest, caring, and present, and to give them the facts about their illness and what can be done for them.

We were asked how we describe "marginal benefit" to patients in our own practice. In this case, "marginal" means additional or incremental. For a Hodgkin lymphoma patient, the marginal benefit is likely years if not a lifetime. For a pancreas cancer patient, the marginal benefit may be weeks or at best a few months. We review how we can explain honestly and efficiently the benefits and options of treatment when the goal is not cure, using chemotherapy for pancreas cancer with erlotinib and gemcitabine as an example.

Do Our Patients Want Us to Be Honest with Them?

For most patients, the answer is an unequivocal yes. However, not all patients do, and there is no way to find out what the patient knows or wants to know without asking directly: “What do you know about your disease? What do you want to know about your disease and its likely course?” Nearly all patients and families will ask you to be honest and direct, even if the news is bad (1). Some patients and families will be unable to reconcile reality and hope, and will ask for information without specific numbers (2), so the only approach must be to ask permission. Some patients will want to negotiate the sharing of information over time, with nearly all patients wanting information at the time of diagnosis, but more information to their caregivers as the terminal illness ensues (3).

Are We Honest with Our Patients? Do They Believe Us?

Oncologists almost always tell a patient if he or she has a curable illness. However, they give specific prognosis information only when asked, in one study about 48% of the
time, and do not routinely give patients an estimated survival time (4).

Patients may believe that the goal of the treatment is to cure the cancer, when the actual goal is palliative. Even if the oncologist tells them, some patients will choose not to believe the information, or interpret it as not applying to them. In two studies separated by 15 years, one third of palliative radiation oncology patients believed they were being treated for cure, when they had been told they had incurable disease (5, 6). In our most recent study, 58% of patients with incurable breast, colorectal, lung, or hormone-refractory prostate cancer thought they could be cured. This number only decreased to about 33% when they were given specific printed information with their own chance of cure (7). The situation is likely similar to that in the intensive care unit, where patients and their surrogates are twice as optimistic as their intensive care unit doctors, even when given real survival numbers. Confidence in the ability of doctors to predict prognosis, alternative belief systems, and lack of trust in doctors all play a major role in not accepting the medical facts (8). This suspension of belief may be different from denial, in that our cancer patients will often make plans for death but not want to dwell on it.

What Are the Medical and Economic Facts about Pancreas Cancer Chemotherapy?

Metastatic pancreas cancer remains an incurable disease with the majority of patients dead at 12 months. The landmark trial that showed an improvement in overall survival and clinical benefit has provided a model for relative, albeit limited, success in treating this cancer (Table 1). To date, no therapy has been proven substantially more effective or less toxic than infusional gemcitabine (9). There has not been a change in population survival with pancreas cancer as seen in breast and colorectal cancer. In fact, recent analyses of Medicare patients with pancreas cancer who did not use hospice versus those who used hospice and no chemotherapy at the end of life showed that those who used hospice actually lived longer: 210 versus 189 days, P = 0.0102 (10). Reasonable explanations include that n-th line chemotherapy and complications actually hastened death, or that the physical and spiritual comfort of hospice prolongs life.

Table 1. The benefits, risks, and costs of treating patients with metastatic pancreas cancer

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Overall Survival</th>
<th>Clinical Benefit*</th>
<th>Significance</th>
</tr>
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<tbody>
<tr>
<td>Gemcitabine versus 5-fluorouracil (29)</td>
<td>Median 5.65 versus 4.41 months (P = 0.0025), 1 year 18% versus 2%</td>
<td>23.8% versus 4.8% (P = 0.0022)</td>
<td>The average person will gain 9 weeks of life.</td>
</tr>
<tr>
<td>Gemcitabine + erlotinib versus gemcitabine alone (30)</td>
<td>Median 6.2 versus 5.9 months (P = 0.038), 1 year 23% versus 17%</td>
<td>No difference in quality of life. Side effects especially rash and diarrhea more common in erlotinib arm.</td>
<td>The average person will gain 2 additional weeks. The marginal CER of erlotinib was $7,885 per week of life saved and $410,000 to $498,379 per year of life saved.</td>
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*Improvement in pain, performance status, or weight without a deterioration in any other factor (31).

With Whom, Where, When, and How Can We Have These Conversations?

Every visit offers an opportunity to have these conversations. Oncologists often say they are too busy to have these conversations, but during the time course of treatment, each clinic visit is a potential. We suspect that oncologists who use the time excuse, similar to those who use it about...
"do not resuscitate" (DNR) discussions that take 6 (15) or 10 (16) minutes, are protecting themselves from the difficult emotional exposure of sharing sad and bad news (17).

A critical, but often overlooked, part of the discussion is the "framing effect," in which people come to different decisions on the basis of how information is presented or framed (18). For example, presenting the results as "a 10% chance of survival" versus a "90% chance of dying" could well be associated with differences in decision making.

Most practitioners and patients prefer to first consider the potential benefits of treatment before discussing the potential harms. In addition, when a choice of two strategies is available, our experience shows that the default is to estimate the largest potential benefit even if it may not be the most likely outcome.

The simplest way to ask is the most direct (19): "Is the treatment giving you enough benefit that you want to continue?" Clinicians often wonder how much information should be given or can be given about the choice of chemotherapy. Studies in multiple countries have consistently shown that patients want to know the truth, but they may have a different perspective than their caregivers. They are far more likely to want treatments with small potential benefit (or even no proven benefit) than their families or their health care providers (20).

We provide a format for the discussion as shown in the Appendix. We developed this format for a randomized trial of insurance types (21) in patients with advanced lung cancer and have found it useful for discussing benefits and risks in an open, honest way. These questions have recently been incorporated into ASCO Decision Making Tools (22) for patients with non–small cell lung cancer and are available to the public on the ASCO website for first- through fourth-line chemotherapy (23). These decision tools are designed for the patient to use with the oncology treatment team.

In this case, we present the known facts fairly and objectively so that patients have several options. In our experience, most patients will opt for chemotherapy, and some good responses will occur. However, at the same time, we have offered a realistic discussion about prognosis and survival such that patients can "Hope for the best, but plan for the worst."

**When Should Chemotherapy Be Stopped, or Not Offered?**

Using non–small cell lung cancer as an example, the National Comprehensive Cancer Center Network guidelines (24) suggests that chemotherapy not be given, and supportive care considered, when the patient no longer has "good" performance status (usually described as Eastern Cooperative Oncology Group [ECOG] 0, 1, and possibly 2) or has progressed on two treatments. As oncologists, we are concerned that nononcologists may recommend hospice too early; there is ample evidence to suggest that second-line chemotherapy improves survival and gives clinical benefit to lung cancer patients with good performance status (25). However, that cannot be said for n-th line chemotherapy, or for patients with poor performance status; in those cases, it is time to stop and have the difficult conversation.

**Should We Hold out Hope of a "Survival Tail"?**

The possibility of a survival tail is very real for patients with resectable cancer. However, for patients with known metastatic disease, our suggested guidance is "It is unlikely that one exists." In the case of pancreas cancer, there is a minimal survival tail and all the patients on both the landmark trials above died by 24 months. In truthfulness, if we point out that some patients will live a lot longer than 6 months, we should also point out that an equal number will live less than 6 months. Robinson and colleagues found that if the oncologist made just positive statements, such as "Well, it could be a lot longer than those 6 months...", then patients had an unrealistic view of their prognosis. If the oncologist made just one negative, but truthful, statement, such as "...but it could be less than 6 months, so we should plan for that, too," patients had a much more realistic viewpoint of their prognosis (26). If patients do not know the prognosis, they cannot plan.

**What Time Frame Should Be Used?**

For pancreas cancer, the time frames of discussion should be from "a few months to one year for most people." The shorter time interval provides a much more realistic anchor of what can be expected from the therapy under consideration.

**Remember, Survival Is Just One Indicator of Benefit**

Should the impact of therapy on cancer symptoms be different than when discussing survival? Benefits in terms of pain and other symptom management may be under-appreciated by nononcologists. The critical point is making the distinction about marginal benefit(s) in treating the cancer, while making the quality of life as rich as possible and minimizing treatment-induced symptoms. Our impression is that because so much of the typical oncologist-patient interaction is about controlling the cancer, that "inactive" therapy is too often associated with abandonment and not being willing or available to deal with changing symptoms.

**Why Should We Have These Conversations?**

We have recently outlined all the good reasons why doctors should have these discussions with their patients who have incurable diseases (27). Briefly, giving honest information is the right ethical, medical, and legal course for patients who want the information. It may keep some patients from receiving treatment that has minimal if any chance of benefit yet substantial harms, and may convince...
some patients to try chemotherapy when it is known to be helpful. As noted above, it may help patients enroll in hospice rather than do n-th line chemotherapy, a strategy that is associated with better survival in several common cancers.

Such conversations will likely increase referrals to hospice, and save money for society. At present, only 37% of U.S. cancer patients could recall their doctor ever telling them they could die of their disease, and only 11% of doctors told their patients about impending death, even when it was imminent. This situation may account for the 20% of U.S. patients receiving chemotherapy in the 14 days before they die. Of note, when the University of Michigan instituted the Quality Oncology Practice Initiative that emphasizes feedback to practices and individuals, the number of solid tumor patients receiving chemotherapy within 14 days of their death fell from more than 50 to 20% (28).

Conclusions

Treatment interventions (usually chemotherapy) in the setting of metastatic cancer with a poor prognosis must be as realistic as possible in the presentation of benefits and harms. Practitioners need to be aware of the impact of how they frame decisions (survival or responses versus death or progression) and discuss the potential harms of therapy as well. For some cancers, there is evidence that people who continue treatment and avoid hospice do not live as long. For many patients, continuing chemotherapy when activities of daily living are compromised is a mistake that directs limited time and energy to an unwinnable battle against the cancer, when time and energy should be directed at life transition planning. For patients wishing to consider additional treatment when the benefits are small, decision aids with graphic representation of anticipated benefits and trade-offs should be encouraged.

Appendix: Decision Aid for a Patient with Metastatic Pancreas Cancer

What is my chance of being alive at 1 year if I take chemotherapy, or do best supportive care such as hospice?

The numbers shown are what happens to the average person with this disease in this situation. Half the patients will do better than this, and half will do worse. The numbers given for the chance of cure are very accurate. The numbers are given to help you with your own decision making.

If you are having symptoms because of the cancer that limit your daily activities, the chances of being alive at 1 year are less than that described above.

Without chemotherapy, about 2 of 100 people would be alive at one year. With chemotherapy, about 18 of 100 people would be alive at one year. The following table gives some estimates from a recent trial of chemotherapy with gemcitabine versus best supportive care, or hospice-type care. The chance of being alive at 1 year was higher with chemotherapy.
People who got erlotinib lived 2 weeks longer, on average. All patients had died by 22 months after start of treatment. If erlotinib is added to gemcitabine, there is more chance for diarrhea, 56% compared with 41%. For the erlotinib patients 72% had some rash, but it was severe in only 6%. Quality of life was the same in both groups, except for the diarrhea.

**Are there other issues that I should address at this time?**

Because this is such a serious illness, and nearly all people die within 2 years, many people use this time to address a life review. That would include what they have learned during life that they want to share with their families, and planning for events in the future like birthdays or weddings.

Some people address spiritual issues.

Some people address financial issues like a will.

Some people address advance directives (living wills). For instance, if you could not speak for yourself, who would you want to make decisions about your care? If your heart stopped beating, or you stopped breathing, because of the cancer worsening, would you want to have resuscitation [cardiopulmonary resuscitation (CPR)], or be allowed to die naturally without resuscitation?

Some people use this time to discuss with their loved ones how they would like to spend the rest of their life. For instance, how and where do you want to spend your last days? Do you want to have hospice involved?

These are all difficult issues, but important to discuss with your family and your health care professionals.

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