Assessing cancer clinical trials: Will your patient benefit from a 'breakthrough'?

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ABSTRACT

Cancer patients and their families often ask their primary care physicians if a new treatment reported in the news can help them. Physicians familiar with the long and complicated process of oncologic clinical trials are in the best position to assess the potential for clinical benefit from a new antineoplastic therapy.

In analyzing 'breakthroughs,' it helps to know about clinical trials

PICK UP A NEWSPAPER or turn on the nightly news, and chances are you will see a story about some breakthrough in cancer treatment. And so will your patients.

Typically, the story is about a novel cytotoxic, cytostatic, immunologic, antiangiogenic, or antimetastatic drug that has been noted to cure tumors in mice and shows "remarkable activity" in early-stage trials in humans. Typically, also, the biotech company that is developing the drug wrote the press release on which the news story is based.

Cancer patients and their families who see the story wonder whether it is relevant to their condition,[1] and so they quickly—often the same day—call a person they know and trust: you, their primary care physician.

How should you respond? What advice should you give?

When trying to analyze, on the patient's behalf, the relevance of reports of breakthroughs in cancer treatment, it helps to understand the process by which new drugs undergo clinical trials in oncology—and of the clinically relevant limitations of the data.

PRECLINICAL MODELS: OF MICE AND TEST TUBES

Laboratory experiments in vitro or in vivo (eg, in mice) can suggest that an agent might be effective and might have tolerable toxicity, but these preclinical models have little, if any, direct clinical relevance.

Several decades of extensive laboratory evaluation have repeatedly confirmed that it is far easier to cure cancer in mice than in man. Furthermore, several years may pass after the initial promising experimental observations before the first patients receive the drug. This delay is due to US Food and Drug Administration requirements that thorough preclinical toxicologic testing be performed to minimize the chances the drug will have severe—or even fatal—adverse effects.[2]

PHASE 1 TRIALS: ESTABLISHING SAFETY

If the new drug makes it out of the laboratory, the next step is one or more phase 1 trials to evaluate its safety and pharmacokinetic properties and determine the best dosage to be used in the next phase of testing (TABLE 1).

For a phase 1 trial (or any trial) to be ethical, the patients have to give their informed consent. They have to understand the legitimate goals of the trial and what they can reasonably hope to get out of it.[3–5] With important exceptions, very few patients (< 5%) in

phase 1 trials derive any objective benefit from the drug tested.[6–8] Nevertheless, patient surveys have clearly documented that patients' major reason for participating in phase 1 trials is to achieve direct clinical benefit.[9]

Although phase 1 trials are not designed to determine if a drug is beneficial, it is relevant to observe patients for evidence of benefit (eg, shrinkage of tumors, improvement in cancer-related symptoms). These types of observations can serve as early indications of possible biologic activity and can help determine if an individual patient should continue the experimental regimen. Such an analysis is consistent with both the scientific objectives of the study and individual patients' goals of receiving benefit.

Phase 1 trials do not prove clinical benefit

Here we encounter our first difficulty with interpreting clinical trial data. If one or more patients show evidence of objective tumor regression (eg, a computed tomographic scan showing that a retroperitoneal lymph node that formerly measured 2 cm × 2 cm now measures 1 cm × 1 cm), it is reasonable to conclude that the drug shows evidence of a biologic effect against cancer. However, is this also evidence of clinical benefit?[10]

Naturally, the patient, family, and physician are delighted if a radiograph shows tumor shrinkage. However, a decrease in the size of a tumor is not synonymous with clinical benefit. Thus, physicians counseling patients interested in news reports of "positive" phase 1 trials need to know that many questions must be asked:

- Was this regression accompanied by improvement of cancer-related symptoms such as pain?
- How long did the shrinkage last?
- If symptoms improved, how long did this improvement persist?
- What toxic effects did this regimen cause?
- Did the patient's overall quality of life improve, worsen, or remain unchanged after treatment?

TABLE 1

Phases of the oncologic clinical trial process

Phase 1 trials
- Primary goals
  - Test the safety and pharmacokinetics of new antineoplastic agents
  - Determine the optimal drug dose and schedule to be used in future clinical trials
- Secondary goals
  - Detect evidence of anticancer activity that may help in the selection of clinical settings for phase 2 testing

Phase 2 trials
- Primary goals
  - Evaluate the objective response rate of an agent in a specific clinical setting (eg, metastatic, previously untreated colon cancer)
  - Gather more information about the toxic effects of an agent
- Secondary goal
  - Examine progression-free and overall survival of the treated population

Phase 3 trials
- Primary goal
  - Directly compare an experimental regimen to a control regimen, ie, a different drug, a different method, a placebo, or observation only; end points can include statistically significant improvements in response rates, survival, toxic effects, or quality of life

PHASE 2: DETERMINING OBJECTIVE RESPONSE

Similar issues arise in phase 2 clinical trials, in which a more homogenous population (eg, a group of patients who all have the same disease in the same tumor stage) all receive an identical regimen, as determined from data obtained in phase 1 studies.

This phase generates more information about toxicity, but the main goal is to examine the drug's extent of activity—the percentage of patients who achieve an objective response.

The question of clinical benefit also is relevant in this setting. Did symptoms improve in patients whose cancer responded to treatment? How long did the symptomatic improvement last? Was the patients' quality of life seriously impaired by treatment-related toxic effects to the point that any improvement in symptoms was nullified? Was information regarding these important issues included in the trial report? If not, why not?

Phase 2 trials do not measure survival

One thing phase 2 trials do not tell us is whether patients survive longer if they receive the new treatment. Unlike phase 3 trials, which I will discuss shortly, there is no direct comparison of the experimental treatment group with a control group who undergoes the current standard therapy.

Oncologic studies often report several survival statistics. *Overall survival* is the time from the start of treatment until death. *Progression-free survival* is the time between the start of therapy and documentation of tumor progression.

In some types of cancer (eg, pancreatic), death usually rapidly follows initial disease progression. However, for others (eg, non-Hodgkin lymphoma), survival may be prolonged despite initial disease progression. This prolonged survival may afford the opportunity to give curative second-line therapy.

Unfortunately, since phase 2 trials do not directly compare an experimental treatment group with a control group, it is rarely appropriate to state that the survival of one population treated in a particular manner is superior to that of another population with the same cancer treated with an alternative approach. This difficulty in comparison is due to several reasons.

Cancer is heterogenous in its natural history, with or without specific therapies.

Selection bias. Oncologists tend to give the more intensive and potentially more complex and toxic treatments to the patients who have the best performance status. This bias occurs because patients with serious comorbid medical conditions or the most serious deterioration of normal daily function are much more likely to experience unacceptable side effects—including death—from these unproven and aggressive management strategies. Thus, often in phase 2 trials the oncologist appropriately decides to avoid such treatments in this population until the potential morbidity or mortality is proven to be justified by superior survival.

Clinical cancer investigators have recognized for more than 40 years that one of the most powerful determinants of survival in a particular setting (eg, stage 4 breast cancer) is the patient's baseline performance status, independent of any specific therapy for the cancer.[11] This finding should not come as a surprise, because complications of the cancer or other intervening disease processes—including death—develop more rapidly in patients with the most extensive symptoms or serious coexisting medical conditions.

In fact, all phase 3 oncologic trials take this critical feature of disease into consideration when formulating stratification strategies for various arms of a study. This potential bias in phase 2 trials introduced by "clinical judgment" on who receives the experimental therapy means that comparing survival between two nonrandomized patient groups may lead to seriously erroneous conclusions.

Thus, physicians need to caution their patients inquiring about reports of a promising new treatment that phase 2 trial survival information needs to be viewed critically.

PHASE 3: MEASURING GENUINE CLINICAL BENEFIT

The gold standard in determining genuine clinical benefit in oncology is the phase 3 or randomized clinical trial, in which patients are randomly assigned to either an experimental treatment group or a control (usual treatment) group. To document that one treatment is better than another, you need evidence that it produces superior outcomes, (ie, longer progression-free or overall survival with acceptable toxicity, or reduced toxicity with the same survival) in appropriately designed and conducted randomized trials.

Contrary to hopes, few patients benefit in phase 1 trials

There are occasional important exceptions to this statement. For example, a phase 2 trial demonstrated that cisplatin-based chemotherapy dramatically alters the cure rate in germ cell malignancies.[12]

Nevertheless, as previously mentioned, the fundamental advantage of phase 3 trials over phase 2 trials (in which the experimental treatment response is compared with historical data) is the elimination of selection bias.

DOES TREATMENT IMPROVE QUALITY OF LIFE?

Until relatively recently, oncologic trials, including phase 3 studies, did not formally examine the impact of specific therapies on

quality of life. A number of validated tools designed to explore this issue now have been shown to be useful in oncology.[13]

Traditionally, high objective response rates to a drug and longer survival rates are seen as measures of benefit; the side effects of therapy are often perceived as unrelated statistics. For example, in a phase 3 trial, the measures of benefit and the percentage of patients experiencing grade 4 bone marrow suppression or mucositis or other side effects are listed separately.

However, the critical question remains: How did the treatment affect the patient? Was the improvement in pain, shortness of breath, abdominal swelling, headaches, weight loss, or other effects of the disease sufficient to offset the required hospitalizations for treatment-related side effects, such as neutropenic sepsis, diarrhea, or peripheral neuropathy?

To optimally examine clinical benefit, a trial must directly address the impact of the treatment on the patient—not only on the tumor. Properly conducted phase 3 trials that demonstrate a favorable impact on overall quality of life as well as survival present the strongest evidence of clinical benefit.

Trials must address the patient—not only the tumor

REFERENCES

1. **Ryan DP, Penson RT, Ahmed S, Chabner BA, Lynch TJ Jr.** Reality testing in cancer treatment: the phase I trial of endostatin. Oncologist 1999; 4:501–508.
2. **Stephens TD, Brynner R.** Dark Remedy: The Impact of Thalidomide and its Revival as a Vital Medicine. Cambridge, Mass: Perseus Publishing, 2001.
3. **Kodish E, Stocking C, Ratain MJ, Kohrman A, Siegler M.** Ethical issues in phase I oncology research: a comparison of investigators and institutional review board chairpersons. J Clin Oncol 1992; 10:1810–1816.
4. **Tomamichel M, Sessa C, Herzig S, et al.** Informed consent for phase I studies: evaluation of quantity and quality of information provided to patients. Ann Oncol 1995; 6:363–369.
5. **Doyle C, Crump M, Pintilie M, Oza AM.** Does palliative chemotherapy palliate? Evaluation of expectations, outcomes, and costs in women receiving chemotherapy for advanced ovarian cancer. J Clin Oncol 2001; 19:1266–1274.
6. **Decoster G, Stein G, Holdener EE.** Responses and toxic deaths in phase I clinical trials. Ann Oncol 1990; 1:175–181.
7. **Von Hoff DD, Turner J.** Response rates, duration of response, and dose response effects in phase I studies of antineoplastics. Invest New Drugs 1991; 9:115–122.
8. **Estey E, Hoth D, Simon R, Marsoni S, Leyland-Jones B, Wittes R.** Therapeutic response in phase I trials of antineoplastic agents. Cancer Treat Rep 1986; 70:1105–1115.
9. **Daugherty C, Ratain MJ, Grochowski E, et al.** Perceptions of cancer patients and their physicians involved in phase I trials. J Clin Oncol 1995; 13:1062–1072.
10. **Markman M.** Clinical response versus clinical benefit in oncology: not necessarily equivalent terms. J Cancer Res Clin Oncol 1997; 123:363–364.
11. **Karnofsky DA, Burchenal JH.** The clinical evaluation of chemotherapeutic agents in cancer. In: Macleod CM, editor. Evaluation of Chemotherapeutic Agents. New York: Columbia University Press, 1948:191–205.
12. **Einhorn LH, Donohue J.** Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 1977; 87:293–298.
13. **Cella DF, Tulsky DS, Gray G, et al.** The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993; 11:570–579.

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