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Clinical Trials: What You and Your Patients Need to Know

Linda H. Yoder

The purpose of the next two *Cancer: Conquering and Caring* columns is to provide nurses with information about clinical trials, such as how to find out about current clinical trials and patient perspectives to consider when discussing clinical trials with patients and/or their family members. In this column, nurses will be introduced to the language of clinical trials and the terminology used in clinical trials, protocols, and consent forms.

The American Cancer Society has a goal of 50% reduction in cancer mortality rates by 2015. To achieve this goal, the emphasis on prevention and early detection must continue, as well as the focus on the development of better treatment modalities. The development and evaluation of new treatments involves a process starting with preclinical research and evolving through phase IV trials. The cancer drug development process can last 10-17 years, with an average of 100 months from bench research to Food and Drug Administration (FDA) approval. The FDA statutes related to new drug development came into effect in 1906. However, it was not until 1962, with the creation of the Kefauver-Harris Drug Amendments, that manufacturers were required to prove that new agents were both safe and effective for their intended use before obtaining marketing approval (Mulay, 2002). More recently, clinical trials also were created to test known agents in new combinations of treatments.

At a time when the number of new agents needing to be evaluated in clinical trials is increasing, there continues to be a limited number of people who participate in these vitally important studies. In a 2000 survey of 6,000 adults, 85% of the respondents said they were unsure or unaware that participation in a clinical trial might have been an option. Additionally, 75% of respondents said they would have enrolled in a clinical trial if they had known it was an option. Of the people who knew that clinical trials were an option but refused to participate, they gave a variety of reasons for not consenting to be in such research: they thought the care they would receive would be less effective than standard care, they were afraid they might be randomly assigned to a placebo arm of a study, they feared being treated like "a guinea pig," or their insurance would not cover the costs. Of those people responding to the survey who had participated in a clinical trial, 97% said they were treated with dignity and respect and the quality of care they received was "excellent" or "good" (Comis, Miller, Aldige, Krebs, & Stoval, 2003; McCabe, 2004). Because there can be a wide range of misunderstanding about clinical trials, it is important that nurses are aware of the basic concepts surrounding clinical trials in order to answer patient/family questions correctly, and to refer patients to correct sites on the Internet and to other appropriate resources.

What Are Clinical Trials?

Oncology clinical trials are prospectively designed research evaluations of new interventions for the prevention, diagnosis, treatment, and/or improvement of quality of life of people at risk for, or diagnosed with, cancer. Clinical trials require detailed scientific planning and rigorous review, conduct, and oversight. Because clinical trials are essentially research studies, they require safeguards for study participants. Therefore, clinical trial subjects usually are required to provide informed consent for their participation, which requires a thorough presentation of the trial procedures, risks, benefits, compensation, and ability to withdraw from the study. Typically, a physician at the medical facility conducting the trial is the site principal investigator. Most clinical trials require large numbers of

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participants in order to generate enough data to draw reliable conclusions. Therefore, many clinical trials are *multi-site,* which means that the same clinical trial is available in multiple locations in the United States and perhaps even internationally. Also, many clinical trials are conducted through *cooperative groups,* which are assembled from a multi-institutional system of academic institutions and cancer treatment centers (McCabe, 2004; Mulay, 2002).

Types of Clinical Trials

The most common type of clinical trial is designed to evaluate new treatments, but as clinical trial research has evolved, studies are more recently being designed to develop interventions across the entire cancer continuum, such as prevention, detection, and palliation (McCabe, 2004).

Prevention trials. These studies are designed to evaluate interventions, such as lifestyle modifications, pharmacologic agents, dietary supplements, and herbal agents for the prevention of cancer in people at risk for developing the disease. An example of a prevention trial might be a study comparing the use of tamoxifen (Nolvadex®)against placebo in women at high risk for developing breast cancer (McCabe, 2004).

Screening and early detection trials. These trials are created to determine if and when we can detect cancer as early as possible in individuals who do not yet have a diagnosis of cancer, but who may be at risk (McCabe, 2004).

Diagnostic trials. These studies are designed to evaluate new tests, interventions, or procedures that can identify suspected cancer earlier or more accurately, or both. Such studies may include recent information learned from the Human Genome Project or laboratory studies evaluating tumor markers' molecular signatures on the cell (McCabe, 2004).

Treatment trials. These trials are designed to evaluate the safety and effectiveness of new drugs, biologic agents, radiation therapy applications/techniques, surgical procedures, and/or behavioral interventions in people with cancer (McCabe, 2004).

Quality of life/Supportive care trials. Such trials are created to determine interventions that may improve comfort and quality of life domains (for example, functional status, psychosocial functioning) that may be negatively affected by cancer and/or cancer treatment modalities (McCabe, 2004).

Phases of Clinical Trials

Clinical trials usually take place in four phases with each phase designed to answer a research question that builds on the findings derived from previous animal studies or from a previous phase of human studies. The concepts described in this column will apply to most types of clinical trials, not just oncology trials. The *research questions* that guide the four phases of clinical trials are similar to (Gulatte & Gaddis, 2005; McCabe, 2004; Mulay, 2002):

Phase I. What is the safest tolerable dose of the agent, how can the agent best be administered, and what effect does the agent have on the body (toxicities, side effects, and/or responses)? Therefore, the researcher seeks to know the safe dose of the drug, the side effects/toxicities, and how the drug is metabolized.

Phase II. What effect does the agent have on a particular type of cancer, and what effect does the agent have on the body?

Phase III. Is the new agent or combination of agents/therapies better than the current standard of care for a particular type(s) of cancer?

Phase IV. What is the long-term safety and effectiveness of the agent/intervention?

Phase I Trials

In most cases, phase I trials are designed to determine the maximum tolerated dose (MTD) and the dose-limiting toxicities of a new agent. Phase I trials are the first time a drug/therapy is being tested in humans. Therefore, what is known about the drug is derived from animal studies and no information about the effective dose or side effects in humans is known. The success of a drug in animal models may not translate directly to humans. Before a phase I trial begins, no one knows whether the drug/agent is safe in humans or if it will have any positive/negative effect. Although the primary goals of phase I trials are to determine pharmacologic behavior, toxic effects, and recommended dosages in future trials, these studies are conducted with a therapeutic intent. The dose of the drug and the administration schedule established in phase I trials will be used in phase II studies. More recently, phase I trials also are conducted to evaluate a new dose and schedule of an approved agent to broaden the application of that drug to a new disease or to further evaluate the agent in populations not previously studied. Some phase I trials examine the interaction between two or more known agents that have not been previously administered in combination. New agents are first tested in adults and then may be followed by testing in pediatric populations (McCabe, 2004; Mulay, 2002).

Most phase I oncology clinical trials are open to patients who have a proven malignancy for which no effective standard therapy currently exists or whose disease is refractory to known therapy. Because of the eligibility requirements for phase I trials, most patients in these trials have been extensively treated with other therapies prior to entering the study or their diagnosis is such that no standard therapy is available for their stage of disease. However, the patients must have adequate major organ function for the drug to be properly metabolized and excreted. In most cases, the study volunteers must have a life expectancy of at least 1-2 months because this is the time frame considered to be the minimum period required to observe toxic effects (McCabe, 2004; Mulay, 2002).

In a phase I study of a new agent, the initial group of volunteers receives a dose that is based on preclinical testing. This dose is usually quite conservative because the clinical researchers realize that animal studies are not perfect predictors of toxicity in humans. Study participants are usually divided into *cohorts* (groups) of three to six people. Each cohort is treated with increasing doses of the new agent and the results obtained with initial cohorts influence the doses that subsequent volunteers receive. If no serious side effects or toxicities are seen in the initial cohort after a period of time (usually 3-4 weeks), the next cohort receives a higher starting dose (McCabe, 2004; Mulay, 2002).

Until recently, the most frequently used research plan for

increasing the dose of the agent (dose escalation) was the modified Fibonacci scheme. This approach sets the second dose level at double the initial dose, the third dose escalation at 67% higher than the second, the fourth escalation 50% higher than the third; and each subsequent level is further increased by 33% of the previous level. Clinical researchers desire to avoid escalating the dose too rapidly (thereby exposing the patient to a severe or even life-threatening toxicity) or too slowly (potentially depriving patients of a possible benefit by essentially giving subtherapeutic doses) (McCabe, 2004).

If a dose causes a severe toxicity in several patients, the study may be stopped at that dosage. The toxicity is referred to as the *dose-limiting toxicity (DLT)* and the dose that preceded the DLT is the *maximum tolerated dose (MTD),* the dose that can be given to humans without unacceptable toxicity. The MTD, which may cause moderate, but reversible toxicity in the majority of patients, is then recommended for further study in a phase II trial. As researchers continue to gain an increasing understanding of the molecular basis of cancer, there may be a shift from using MTD as the phase I endpoint to a method of establishing an "optimal biologic dose" as the endpoint. Such an endpoint is established as the safe dose of the agent found to affect a specifically defined target in the tumor (McCabe, 2004; Mulay, 2002).

Predicting how many patients will be in a phase I trial or exactly when each cohort will begin is very complex. It is possible that the DLT may occur after only 15 patients, or it may not occur until 100 patients have taken the drug. If, at any time, there are concerns about the safety of an agent or treatment, the trial may be stopped while the clinicians/scientists try to obtain a clearer understanding of the situation. Patient safety should be the primary concern (McCabe, 2004; Mulay, 2002).

Phase II Trials

Phase II trials are developed to evaluate the efficacy of an agent against specific types of malignancies, using the dose and schedule found to be safe in phase I trials. Additionally, phase II trials target cancers that demonstrated some level of response in the phase I trial and for which there is no effective standard therapy. Participants must have a specific diagnosis and measurable disease. Also, patients should have good performance status and minimal prior exposure to chemotherapy. In many cases, one or two prior regimens of therapy are allowed. In patients heavily pretreated with chemotherapy, a drug may not demonstrate its true activity; the problem is that patients who have failed standard therapy may be the least likely individuals to provide the best evaluation of the new agent. Patients also must have adequate organ function and a life expectancy of at least 3 months to participate in most phase II clinical trials (McCabe, 2004; Mulay, 2002).

In the majority of phase II trials, all subjects receive the same dose of the new agent (or undergo the same new intervention). The new therapy is assessed for efficacy and additional side effect/safety information is obtained. Some phase two studies compare different time schedules of administering the agent. When phase II trials consist of such a comparison design, the subjects are randomly assigned into one treatment group or the other (often called *treatment arms*). At the conclusion of such studies, the most promising regimen is selected to move into phase III trials (McCabe, 2004; Mulay, 2002).

As with phase I trials, drawing conclusions from phase II trials is usually complex. The typical measure of a new therapy's antitumor activity is the *response rate.* It is important to remember that although determining the response rate may answer the primary research question in the clinical trial, a partial response may not necessarily signal patient benefit in the long-term. A partial response (50% reduction in tumor mass) may be brief and complicated by side effects/toxicities. If the new therapy does seem to demonstrate activity against the malignancy, it continues to require further testing, because at this point the new therapy has not been compared to any other agent or intervention; therefore, its relative value is uncertain. Additionally, phase II studies are too short to determine long-term benefits, such as overall survival (McCabe, 2004; Mulay, 2002).

Phase II trials also may be used to evaluate the practicality and tolerability of combination therapy (when multiple drugs or interventions are used together). Again, the results of these types of phase II trials can be extremely difficult to interpret because in many cases the drugs being evaluated are known to be of some benefit alone, but their combined use is under scrutiny. In such cases, the combination of agents/interventions must show greater activity/results than the individual components or a standard therapy combination regimen (McCabe, 2004).

For molecularly targeted therapies under development, determining antitumor effects in phase II trials involves using either the MTD or the biologically active dose. Patient selection is similar to that of other phase II trials but with more rigorous criteria to enroll people with tumor types that possess the target of the molecular agent under investigation. These types of phase II studies include endpoints such as response rate, side effects, toxicities, and tumor analyses to determine the level of response at the molecular level (McCabe, 2004).

In the next installment of *Cancer: Conquering and Caring* (December 2005), phase III and phase IV trials will be discussed, as well as preventive studies. Other columns will be devoted to the informed consent in clinical trials and patient decision-making in regard to clinical trial participation. Please continue to read and inform your colleagues and patients about this important information! ■

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CE SERIES

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Clinical Trials: What You and Your Patients Need to Know

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Answer Form:

1. If you applied what you have learned from this activity into your practice, what would be different?

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Evaluation	Strongly disagree				Strongly agree
The offering met the stated objectives.					
2. By completing this activity, I was able to meet the following objectives:					
a. Discuss the purpose of clinical trials.	1	2	3	4	5
b. List types of clinical trials.	1	2	3	4	5
c. Describe phase I and phase II of clinical trials.	1	2	3	4	5
3. The content was current and relevant.	1	2	3	4	5
4. The objectives could be achieved using the content provided.	1	2	3	4	5
5. This was an effective method to learn this content.	1	2	3	4	5
6. I am more confident in my abilities since completing this material.	1	2	3	4	5

7. The material was (check one) ___new ___review for me

8. Time required to complete the reading assignment: _____minutes

I verify that I have completed this activity (Signature):

_____

Comments

_____

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Objectives

This educational activity is designed for nurses and other health care professionals who care for and educate patients and their families regarding cancer clinical trials. For those wishing to obtain CE credit, an evaluation follows. After studying the information presented in this article, the nurse will be able to:

1. Discuss the purpose of clinical trials.
2. List types of clinical trials.
3. Describe phase I and phase II of clinical trials.

CE Instructions

1. To receive continuing education credit for individual study after reading the article, complete the answer/evaluation form to the left.

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