Special Article

Phase I Cancer Trials and Palliative Care: Antagonism, Irrelevance, or Synergy?

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Abstract

This article synthesizes the presentations and conclusions of an international symposium on Phase 1 oncology trials, palliative care, and ethics held in 2014. The purpose of the symposium was to discuss the intersection of three independent trends that unfolded in the past decade. First, large-scale reviews of hundreds of Phase I trials have indicated there is a relatively low risk of serious harm and some prospect of clinical benefit that can be meaningful to patients. Second, changes in the design and analysis of Phase I trials, the introduction of "targeted" investigational agents that are generally less toxic, and an increase in Phase I trials that combine two or more agents in a novel way have changed the conduct of these trials and decreased fears and apprehensions about participation. Third, the field of palliative care in cancer has expanded greatly, offering symptom management to late-stage cancer patients, and demonstrated that it is not mutually exclusive with disease-targeted therapies or clinical research. Opportunities for collaboration and further research at the intersection of Phase 1 oncology trials and palliative care are highlighted. J Pain Symptom Manage 2016;52:437–445. © *2016 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Palliative care, Phase I clinical trials, cancer, ethics, informed consent, end-of-life care

Introduction

The ethical and clinical issues regarding early-phase cancer trials have been debated for more than two decades.[1–10] They include concerns that desperate patients may regard Phase I trials as therapeutic and that researchers could reinforce this misconception by de-emphasizing the trials' true intent to study the safety of investigational agents. Recent early-phase trials demonstrating remarkable therapeutic response[11] may have increased patient perception that Phase I clinical research is an extension of clinical care.[12,13] At the same time, the field of palliative care (PC) has grown rapidly, is now recognized as a specialty, and randomized trials have documented several improved clinical outcomes with PC.[14–19] Consequently, experts and professional organizations have recommended increased integration of oncology care and PC early in the illness of patients with metastatic cancer.[20,21] Extension of this simultaneous, integrated care model to patients in early-phase trials may address some of the central clinical and ethical challenges surrounding Phase I trials. Although PC and Phase I trials were considered to have a dichotomous

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relationship in the past, the changing nature and expansion of both fields have started to transform this relationship.[22] We recently convened an international panel of experts to discuss this shift in Phase I oncology and PC science and the implications for clinical care and ethics.

Ethical Challenges

Informed Consent

Key aspects of informed consent for patients enrolling in clinical trials are the assessment of potential harms and their probability of occurring, set against the potential benefits and their probability. Early-phase oncology trials are an important step in developing more effective therapies for treating individual cancers. Yet these trials promise little or no direct clinical benefit to those who participate in them. Because these trials are designed to test toxicity rather than the efficacy of investigational agents, patients should expect to incur some risks and no or little clinical benefit from participating. However, a significant body of research indicates that many participants believe that they will experience a substantial personal health benefit by enrolling.[23–26] This fact has been a source of concern for ethicists and researchers.

Of particular concern is the impact high patient expectations have on informed consent to participate in this form of research. Early studies[27] focused on the possibility that patients have an inadequate understanding of the nature of the trials in which they participate. Many participants seem to be under the so-called "therapeutic misconception." They believe incorrectly that the primary purpose of Phase I trials is to provide them with direct clinical benefit rather than advancing generalizable scientific knowledge.[28] Later research suggests that patients in Phase I oncology trials simply miscalculate their own prospects for benefit, although they fully understand the nature and purpose of research. This misunderstanding is referred to as the "therapeutic misestimation."[29] However, in recent years, researchers have begun to investigate the possibility that high expectation for personal benefit in these trials does not reflect any deficit in understanding at all. Rather, in reporting high expectations for benefit, patients may be expressing optimism about their participation in the trial. This phenomenon has been termed "therapeutic optimism."[30,31] Some writers have suggested that therapeutic optimism is mere hopefulness. On this view, patients are not reporting expectations for benefit at all, but rather are making statements about what they hope will happen.[32–34] This explanation overlooks evidence that indicates that therapeutic optimism reflects a bias that distorts the processing and appreciation of risk-benefit information. This bias is referred to as "the optimistic bias" or "unrealistic optimism."[35] This bias has not generally been correlated with a hopeful outlook on life and has been found to be consequential for behavior.[36] All these explanations for why patients might report high expectations for personal clinical benefit from participating in Phase I cancer trials raise concerns about the quality of their consent to participate in research.

Vulnerability, Autonomy, and Nonmaleficence

Other important ethical issues regarding Phase I trials include the perceived vulnerability of patients and the need to promote their well-being while respecting their autonomy. Patients who are referred to participate in a Phase I study face challenging decisions, having to weigh potential benefits of a new investigational intervention and unknown side effects including potential harm. Patients considered for enrollment into these studies have commonly undergone exhaustive anticancer therapies, and in most cases, standard treatments have failed to work. In addition, a considerable amount of patients are suffering from long-term adverse events related to previous therapies, including neuropathy, alopecia, and bone marrow toxicity or they have symptoms related to their underlying disease. Interestingly, despite these side effects, patients with a history of systemic therapy may be more likely to enroll in Phase I trials than those who have not received systemic therapy.[37]

Because impaired physical, emotional, and social functioning have all been associated with therapeutic misconception, Phase I trial candidates may need additional care to avoid this form of misunderstanding.[38] Expressions of therapeutic optimism by these candidates, when it reflects optimistic bias and not mere hopefulness, should also be of concern. Although the risks to these patients should not be discounted, neither should they be overprotected. Patients may want to participate in research for personal and altruistic reasons.[39] Participants in later stage trials commonly report that altruism contributed to their decision to enroll, but participants in Phase 1 trials rarely report altruism as their primary motivation for study participation.[40]

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The potential "relevance" of PC for Phase I participants is based on their prognosis and symptom burden. Patients enrolled in Phase I trials have a median survival of about nine months[41,42] and are likely to be symptomatic from their disease or previous treatments. Patients have traditionally exhausted conventional therapy and later-phase clinical trial options. These are precisely the same characteristics of many patients referred to