The Oncologist®

Editorial

Communicating About Phase I Trials: Objective Disclosures Are Only A First Step

ANNE LEDERMAN FLAMM,[a] REBECCA D. PENTZ[b]

[a]Center for Ethics, Humanities & Spiritual Care, Cleveland Clinic, Cleveland, Ohio, USA; [b]Emory School of Medicine, Emory University, Atlanta, Georgia, USA

Disclosures: Rebecca D. Pentz: Expert testimony: Pfizer. The other author(s) indicated no financial relationships.

In a recent issue of ***The Oncologist***, Fallowfield et al. [1] responded to long-standing and ongoing concerns that flawed understanding and expectations drive patients' agreements to participate in early-phase cancer clinical trials. As it has evolved from its first use 30 years ago [2], the term "therapeutic misconception" (TM) captured the discomfiting notion that patients perceive and seek potential personal benefit arising from early-phase trial participation when in fact such trials are neither designed nor likely to benefit participants. The vulnerability of the affected population, patients who face imminent death from cancers for which no established treatment exists and who rely on oncology professionals for treatment options, fueled ethical concerns that the medical research community, even inadvertently [3], misled desperate patients [4, 5] and implicitly promised potential benefit [6] when recruiting for trials. Studies showing the prevalence of inaccurate assessments (by both patients and physicians) of benefits and risks, hope for personal benefit as patients' reason for joining, and patients' trust in oncology physicians and researchers [7, 8] spurred [9, 10] and continue to incite [11] ongoing efforts within the cancer research community to unearth and redress shortcomings in communication and the informed consent processes when recruiting patients for early-phase trials.

Members of the Fallowfield research team previously observed and analyzed actual consent discussions between oncologists and patients considering phase I trial participation [12]. Identifying omissions of key information such as a discussion of prognosis and alternatives, including supportive care, to trial participation, Fallowfield et al. [1] developed an educational initiative for physicians and other health care professionals (together, HCPs) responsible for recruiting patients to early-phase cancer clinical trials. Their 1-day workshop specifically aimed to enhance HCPs' self-efficacy and the quality of their communication in this endeavor. The intervention produced significant improvements in HCPs' confidence and ability to convey several key disclosure elements, as assessed by coder–investigators and by actor–participants who simulated prospective early-phase trial participants in pre- and post-intervention discussions.

Amid ever-increasing acknowledgment of the importance of HCP communication in enhancing patient satisfaction and the quality of health care [13], the achievement of communication quality improvement by Fallowfield et al. [1] is particularly laudable in light of the historical focus on HCPs' role in TM. Their success exemplifies the positive, if incremental, impact well-designed and well-executed initiatives can have on HCPs responsible for providing critical information to patients considering participation in early-phase cancer clinical trials. Metrics included HCP participants' assessments of self-confidence in early-phase trial discussion, investigators' own blinded pre- and post-intervention evaluations of HCP participants' communication about the trial, and ratings from the simulated patients who received the information.

HCPs' confidence in their abilities is an important metric in the pursuit of improved communication about early-phase trials. Physicians' lack of confidence in their own communications skills may lead to distancing from patients and avoidance of emotionally difficult discussions [14], whereas even brief workshops geared toward physicians' communication skills in sensitive arenas have been shown to result in an increase in the acquisition of such skills and their confidence to use them in clinical encounters [15]. Self-efficacy alone, however, is an inadequate foundation

Correspondence: Anne Lederman Flamm, J.D., Department of Bioethics, Center for Ethics, Humanities & Spiritual Care, Cleveland Clinic, 9500 Euclid Avenue/JJ60, Cleveland, Ohio 44195, USA. Telephone: 216-636-0287; Mobile: 216-312-9528; Fax: 216-444-9275; e-mail: flamma@ccf.org. Received March 15, 2012; accepted for publication March 16, 2012; first published online in ***The Oncologist Express*** on April 4, 2012. 1083-7159/2012/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2012-0107

for positive conclusions about qualitative improvement in skills. The "arrogance-ignorance paradox" [16], the tendency not to recognize shortcomings in one's own knowledge, has been recognized in numerous areas of medical practice, such as pain management [17] and end-of-life care [18], that have been resistant targets of repeated calls for improvement. Sharing such a profile, communication about early-phase trials presents risk that HCPs' self-confidence poorly reflects their actual competence. Additionally, the investigators' earlier work, identifying differences between what oncologists believe they said about key elements and what patients believe they heard, further highlights self-perception challenges. Thus, the inclusion by Fallowfield et al. [1] of structured assessments from both investigators and their simulated patients substantiates that HCPs did in fact discuss more of the required disclosure elements. Achievement of statistical significance on a number of targeted elements, including discussion of symptom control and allowing time for consideration, imparts objective confidence that the workshop enhanced HCPs' ability to convey needed disclosures to patients.

The use of patient simulators by Fallowfield et al. [1] is perhaps more valid than reliance on patients to report discussion content. As the authors point out, although simulators may lack authenticity, they may offer more informed and specific feedback and objective evaluation to enhance learning among HCPs. Moreover, healthy volunteers have been shown to retain the most information about risks and side effects; severely ill phase I participants retain the least [19]. Thus, simulated patients may be better suited than phase I candidates to assess the presence or absence of the study's required disclosures.

The Fallowfield et al. [1] study also reflects sensitivity to the difficult but crucial issue of how requisite disclosure elements are framed, though their approach invites caution that positive results might mask biased presentation. Several key elements, such as checking patients' understanding of prognosis and noting extra burdens of trial participation, aim not only at accuracy but also at offsetting unrealistic expectations patients may have. Moreover, the description of the workshop states that HCPs were encouraged to consider how they structured discussions; investigators then note in the discussion section that the majority of participants had restructured the order in which information was presented pursuant to recommendations arising in the workshop and had spent more time on key elements that counter unrealistic expectations (e.g., awareness of prognosis, understanding of trial aims, and the low likelihood of benefit). Though these data points were not included in the results, they reflect investigators' attention to framing.

Scoring only for the presence of key elements, however, leads to ambiguity in results. Consider the possibility that, taking examples from another observational study of phase I discussions, HCPs center "discussions about prognosis on how many study participants had responded to treatment and the promise of potential benefit"; depict the option of supportive care in opposition to "expressions of [their] optimism about the trial through words, such as 'novel and promising', and by terms, such as 'we're excited' (about the potential efficacy)" and the "urgency for patients to join the trial by indicating the 'scarcity of spots'" available; or mention patients' ability to drop out at any time amid assurances that, otherwise, patients "would continue in the study until the cancer stopped responding to the experimental treatment" [10]. Under the methodology of Fallowfield et al. [1], such discussions would be credited for the requisite disclosure elements despite the highly persuasive framework.

The evolution of research in TM suggests that a limited focus on HCPs' objective disclosures of specific trial-related information as the key to improving patients' decision-making about early-phase trial participation risks oversimplifying or missing ethically critical insights. Since the identification of TM first sparked concern, multiple avenues of research have exposed nuances that defy a simple explanation based on researchers' failure to provide objective and accurate information about early-phase trials' purposes and minimal benefits. Study of TM has distinguished therapeutic misestimation, identifying the chance of personal benefit as greater, or the risk for harm as less, than it actually is [20], from TM. Rather than reflecting patients' receipt of misinformation, discordance between patients' estimates and figures deemed "actual" by researchers may fail to recognize different definitions of benefit. For example, the 5% response rate commonly cited [21, 22] for Phase I trials would not include psychological benefits patients might anticipate [8]. Further scrutiny of TM has also exposed that patients ascribe alternative purposes to conveying factual or cognitive understanding in their estimates, such as registering their optimism or expressing a positive attitude [23]. In other words, patients' expectations for personal benefit may not be knowledge claims but assertions of feelings—of confidence, of optimism, of hope. TM research has also distinguished therapeutic optimism, characterized by some as a positive coping mechanism derived from an individual's natural or circumstantial disposition [24]; others conclude that such optimism is an unrealistic bias that impairs judgment [25]. Very recent research identified a substantial minority of pessimists who perceive their chance of benefit as lower than the rest of the population but join anyway [26].

However difficult "fixing" TM through HCP communication may be, it is a less complex and difficult challenge than comprehending the perspective and role of the other person in the room: the patient who faces imminent death from terminal cancer. A recent attempt to describe the decision-making process in patients considering participation in phase I cancer clinical trials concludes that they are "searching for a way to live to the end" [27]. Researchers relied on the following quote to reflect the perspective of those who joined the trial:

"I can abandon living. But it is also a terrible experience if I abandon living. So I take a gamble of having the possibility of

living because I will suffer whether I am living or abandoning living."

Early-phase trial candidates are influenced not only by rational comprehension of facts but by their psychology, their values, and their hopefulness. As difficult as it is, fairly imparting accurate information is perhaps the lowest-hanging fruit on the tree of HCPs' responsibilities in discussing early-phase trials with patients. Appreciating the impact of patients' circumstances and incorporating their perspectives into recommendations for next steps are much harder tasks.

Author Contributions

Conception/Design: Anne Lederman Flamm, Rebecca D. Pentz
Manuscript writing: Anne Lederman Flamm, Rebecca D. Pentz
Final approval of manuscript: Anne Lederman Flamm, Rebecca D. Pentz

References

1. Fallowfield LJ, Solis-Trapala I, Jenkins VA. Evaluation of an educational program to improve communication with patients about early-phase trial participation. ***The Oncologist*** 2012;17:377–383.

2. Appelbaum PS, Roth LH, Lidz C. The therapeutic misconception: Informed consent in psychiatric research. Int J Law Psychiatry 1982;5:319–329.

3. Emanuel EJ. A phase 1 trial on the ethics of phase 1 trials. J Clin Oncol 1995;13:1049–1051.

4. Miller M. Phase 1 cancer trials: A crucible of competing priorities. Int Anesthesiol Clin 2001;39: 13–33.

5. Annas G. Changing landscape of human experimentation: Nuremberg, Helsinki, and beyond. Health Matrix 1993;92:119.

6. Kodish E, Stocking C, Ratain MJ et al. Ethical issues in phase 1 oncology research: A comparison of investigators and institutional review board chairpersons. J Clin Oncol 1992;10:1810–1816.

7. Meropol NJ, Weinfurt KP, Burnett CB et al. Perceptions of patients and physicians regarding phase 1 cancer clinical trials: Implications for physician-patient communication. J Clin Oncol 2003;21:2589–2596.

8. Daugherty C, Ratain MJ, Grochowski E et al. Perceptions of cancer patients and their physicians involved in phase 1 trials. J Clin Oncol 1995;13: 1062–1072.

9. Daugherty CK. Impact of therapeutic research on informed consent and the ethics of clinical trials: A medical oncology perspective. J Clin Oncol 1999; 17:1601–1617.

10. Joffe S, Cook EF, Cleary PD et al. Quality of informed consent: A new measure of understanding among research subjects. J Natl Cancer Inst 2001;93: 139–147.

11. Brown R, Bylund CL, Siminoff L et al. Seeking informed consent to phase I cancer clinical trials: Identifying oncologists' communication strategies. Psychooncol 2011;20:361–368.

12. Jenkins V, Solis-Trapala I, Langridge C et al. What oncologists believe they said and what patients believe they heard: An analysis of phase I trial discussions. J Clin Oncol 2011;29:61–68.

13. Baile WF, Aaron J. Patient-physician communication in oncology: Past, present, and future. Curr Opin Oncol 2005;17:331–335.

14. Baile WF, Lenzi R, Kudelka AP et al. Improving physician–patient communication in cancer care: Outcome of a workshop for oncologists. J Cancer Educ 1997;12:166–173.

15. Baile WF, Kudelka AP, Beale EA et al. Communication skills training in oncology: Description and preliminary outcomes of workshops on breaking bad news and managing patient reactions to illness. Cancer 1999;86:887–897.

16. Von Roenn JH, von Gunten C. The care people need and the education of physicians. J Clin Oncol 2011;29:4742–4743.

17. Breuer B, Fleishman SB, Cruciani RA et al. Medical oncologists' attitudes and practice in cancer pain management: A national survey. J Clin Oncol 2011;29:4769–4775.

18. von Gunten CF. Arrogance ignorance paradox. J Palliat Med 2005;8:898–899.

19. Shaeffer MH, Krantz DS, Wichman A et al. The impact of disease severity on the informed consent process in clinical research. Am J Med 1996;100: 261–268.

20. Horng S, Grady C. Misunderstanding in clinical research: Therapeutic misconception, therapeutic misestimation and therapeutic optimism. IRB 2003; 25:11–16.

21. Decoster G, Stein G, Holdener EE. Responses and toxic deaths in phase I clinical trials. Ann Oncol 1990;1:175–181.

22. Roberts TG Jr, Goulart BH, Squitieri L et al. Trends in the risks and benefits to patients with cancer participating in phase 1 clinical trials. JAMA 2004;292:2130–2140.

23. Weinfurt KP, Seils DM, Tzeng JP et al. Expectations of benefit in early-phase clinical trials: Implication for assessing the adequacy of informed consent. Med Decis Making 2008;28:575–581.

24. Cohen L, de Moor C, Amato RJ. The association between treatment-specific optimism and depressive symptomatology in patients enrolled in a phase I cancer clinical trial. Cancer 2001;91:1949–1955.

25. Jansen LA, Appelbaum PS, Klein WM et al. Unrealistic optimism in early-phase oncology trials. IRB 2011;33:1–8.

26. Pentz RD, White M, Harvey RD et al. Therapeutic misconception, misestimation and optimism in participants enrolled in phase 1 trials, Cancer 2012 Jan 31 [Epub ahead of print]. doi: 10.1002/cncr.27397.

27. Kohara I, Inoue T. Searching for a way to live to the end: Decision-making process in patients considering participation in cancer phase I clinical trials. Oncol Nurs Forum 2010;37:E124–E132.

See the accompanying article in ***The Oncologist***, volume 17, number 3, 2012.