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IN THE LITERATURE

After Equipoise: Continuing Research to Gain FDA Approval

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Krill LS, Adelson JW, Randall LM, Bristow RE. Clinical commentary: medical ethics and the ramifications of equipoise in clinical research. Is a confirmatory trial using a non-bevacizumab containing arm feasible in patients with recurrent cervical cancer? *Gynecol Oncol*. 2014;134(3):447-449.

"First, do no harm." On the surface, this is the most well-known, easy to understand, and easy to follow mandate given to us as we evolve into doctors. Of course a doctor should do no harm. Quite the opposite—a doctor is meant to care for, heal, and generally do *good*. Most of us chose this career specifically so that we might have that opportunity each day. In medical ethics classes, we learned the basic principles of ethical health care: respect for autonomy, nonmaleficence, beneficence, and justice. As we mature from early medical students to clinical medical students, residents, attending physicians, and perhaps researchers, so does our understanding of these principles and what it means to put them into practice.

In the world of clinical research, the principle of equipoise is basically an application of the principle of nonmaleficence to the process of comparing medications and treatments. It means that, for a study to be ethical, an individual researcher must truly not know whether one treatment has advantages over another when enrolling patients and conducting research [1]. This idea was first proposed by Charles Fried in his 1974 book *Medical Experimentation: Personal Integrity and Social Policy* [2]. It was expanded upon by Benjamin Freedman in his 1987 essay, "Equipoise and the Ethics of Medical Research," in which he proposed that, for a study to be ethical, it's more important for the expert medical community, rather than for an individual researcher, to be in a state of uncertainty regarding the superiority of one treatment or another [3].

In the article to which I am responding [4], Krill and colleagues discuss the Gynecological Oncology Group (GOG) 240, a phase-3 clinical trial in which the antiangiogenesis agent bevacizumab was added to cytotoxic chemotherapy regimens to treat recurrent, metastatic, and persistent cervical cancer. During the second interim analysis, the bevacizumab arms of the study demonstrated significantly improved overall survival of three months compared to chemotherapy alone, regardless of the cytotoxic chemo agents with which they were paired [5].

The National Comprehensive Cancer Network (NCCN) updated its clinical practice guidelines to include bevacizumab for the treatment of advanced cervical cancer, which qualified it for coverage by most private US insurance companies [4]. The National Health Service of England also approved bevacizumab as a first-line treatment. But the US Food and Drug Administration (FDA), which requires more extensive study before approving an agent, was not so quick to accept this modification to approved regimens [4]. Since the Krill et al. article was published in June 2014, the FDA evaluated the use of bevacizumab under its priority approval program and ultimately added recurrent, persistent, or metastatic cervical cancer as indications for use in August 2014 [6]. But let's suppose for a moment that it hadn't.

This lack of approval would have meant that Medicare and Medicaid patients with recurrent, metastatic, or persistent cervical cancer could not have obtained coverage for bevacizumab [4]. For those in the United States without private insurance, this agent is surely cost-prohibitive; a single dose costs several thousand dollars [7]. To close this gap in coverage would require gaining FDA approval through more study. Without FDA approval and subsequent coverage by Medicare and Medicaid, the disparity in outcomes between the privately insured and everyone else would remain. Conversely, continuing the investigation of the safety and efficacy of bevacizumab to facilitate FDA approval and effectively improve access for a broader range of patients would require researchers to subject some participants to chemotherapy alone, expecting that their survival time would be shorter than that of the participants in the experimental arm. Such an arrangement would directly violate the fundamental principle of equipoise [2-4].

In imagining that bevacizumab had not gained FDA approval, my first reaction to the Krill et al. article was in favor of continued investigation of bevacizumab for cervical cancer, so that it might become FDA-approved and therefore available to more patients. I doubt the concept of equipoise was ever meant to limit research in such a way that populations of people would be excluded from the progress generated by clinical trials. It's reasonable to assume that the principle of equipoise was introduced to hold researchers and physician-researchers accountable and prevent them from conducting sham trials with predictable outcomes just to get a "positive" result published. This principle also acknowledges the tremendous value of the countless anonymous patients whose participation, and sometimes deaths, provide answers, warnings, and hope for countless more patients who will benefit from the lessons learned and therapies developed.

On the other hand, what is the value, for lack of a better word, of three additional months' survival? What was the content and quality of those extra three months for patients and their families? Did the majority of patients experience three pain-free, carefree months of checking things off their proverbial bucket lists and soaking in precious moments with their favorite people? Or were they three months filled with doctors' office waiting rooms, mounting medical bills, artificial nutrition, infections,

leaking ostomies, and untreatable pain? If they could tell us, would those who experienced the latter want to live those three months again? Are Medicare, Medicaid, and uninsured patients really missing out on much?

Of course these questions can only be answered by an individual patient in the context of his or her own beliefs, priorities, and values. It's almost certainly my perspective as a young, able-bodied person at this point in time that suggests to me that only three months enjoyed with friends, family, and adventure are worth living. But perhaps the point is that each patient is entitled to the option of the treatment that might give him or her those three months, whatever they may bring, regardless of socioeconomic and insurance status. Ultimately, I can't condone the idea of denying people access to these treatments.

Had FDA approval not been gained, which of the two options would have posed less harm: To have discontinued the study of bevacizumab in the treatment of advanced cervical cancer, which would have precluded FDA approval and subsequently left an entire group of people—those without private health insurance—without access to a treatment for an indefinite period of time? Or to have continued to study how chemotherapy *with* bevacizumab compared to chemotherapy *without* it, thereby directly violating the standard of equipoise. Neither of these options is acceptable.

Thankfully, in the case of bevacizumab, we didn't have to settle for either. However, there will be another case like this, where the various sectors that make up the medical community struggle to agree on a best course of action and where the path that "does no harm" is not quite as clearly defined as it once seemed. Just as physicians and researchers must make it a priority to do no harm, so must the governing and regulating bodies who establish the policies and protocols to which we must adhere.

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