



Access to Investigational Interventions Outside of Clinical Trials: Policy Statement

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Position

Access to investigational interventions outside of clinical trials undermines the clinical trials system and the principle of evidence-based medicine. It has the potential to seriously harm individuals and raises important issues of fairness. For these reasons, the National Breast Cancer Coalition (NBCC) believes that access to investigational interventions outside of clinical trials should be allowed only in very limited circumstances.

Background

NBCC strongly supports the concept of evidence-based medicine.¹ We need to learn what works for women with and at risk for breast cancer, and all women need access to what current scientific evidence indicates is the most effective care available.

There currently is no certain cure for breast cancer, and too few truly effective treatments. For those who have run out of treatment options, the research process seems agonizingly slow. But while the public is inundated with information about cancer “breakthroughs” and news of promising new drugs and procedures, the reality is that most new interventions do not turn out to be effective, or they provide only incremental benefits. Pharmaceutical and other companies, scientists and the media each bear responsibility for creating unreasonable expectations about unproven therapies. These circumstances have created a climate where many patients believe that access to an investigational intervention is their best hope, when most often it is a false hope.

Expanded access (also called compassionate use) is the use of an investigational drug outside of a clinical trial to treat a patient with a serious or immediately life-threatening condition who has no comparable or satisfactory alternative treatment options.² According to a 2009 Food and Drug Administration (FDA) investigational new drug application (IND) regulation, expanded access to investigational drugs for treatment use will be available to:

- individual patients, including in emergencies
- intermediate-size patient populations
- larger populations under a treatment protocol or treatment investigational new drug application²

What Is the Harm of Expanded Access?

It seems compassionate to argue that investigational therapies should be available to seriously ill individuals for whom there is no known effective treatment. However, doing so has significant negative consequences for all breast cancer patients.

First, investigational treatments made available outside of clinical trials undermine the clinical trials system. Clinical trials test new therapies in a systematic and controlled way. They are how we find effective treatments and they are the only way we will ever find a prevention and cure for breast cancer. If a patient can obtain an investigational therapy outside of the trial, there is little incentive for her to participate in a clinical trial. This makes trial accrual difficult, and may significantly undermine the ability of investigators to determine the safety and efficacy of the intervention. This was certainly the case with high-dose chemotherapy with bone marrow transplant for breast cancer. Because this procedure was so widely available outside of clinical trials, it was extremely difficult to accrue patients to trials. It took many years longer than it should have to complete the clinical trials, which told us that the high-risk, grueling and expensive procedure is no more helpful to women with breast cancer than standard chemotherapy regimens.³

Second, access to investigational interventions outside of clinical trials undermines the principle of evidence-based medicine. Evidence-based medicine means using medical research—information about other patients that has been systematically collected and analyzed—to determine what is most likely to help an individual patient.

Without evidence, health care providers have no good way of knowing what does and does not work. They could use the trial and error approach, learning from their previous patients, but this approach to research lacks statistical power and the ability to control for external factors that might influence their patients' outcomes. The more patients involved in a controlled study, the more likely the results from that study will be correct. A “study” of five breast cancer patients means nothing. When a patient gets an investigational intervention outside of a clinical trial, it is no longer an investigation, because one patient's experience by itself tells us nothing. It is only when patients are part of well-designed, high quality medical research that we add to the body of evidence and can move forward in breast cancer care.

Third, access to investigational interventions outside of clinical trials may be harmful to patients. It is impossible to know the risks of a new intervention, much less the possible benefits, if it has never been studied systematically in a clinical trial. Even when properly studied, significant safety issues often do not emerge until well into a phase III clinical trial. For example, the heart damaging effect (cardiotoxicity) of the drug Herceptin was not apparent in the phase II data, but emerged in the much larger phase III trial.⁴

Investigational treatments are not miracle cures. They are by definition untested and it is possible -- indeed, very likely -- that an investigational therapy will be ineffective. The large majority of so-called “promising” new therapies never make it to market either because they are too dangerous or, more likely, they just don't work.

Fourth, off-trial access to investigational interventions raises serious issues of fairness. The availability of these therapies is usually severely limited by practical and economic constraints. As described in the 2009 FDA regulation², individual patients sometimes gain access through single-patient IND applications, a practice also known as “compassionate access”. These patients are usually very knowledgeable and well-connected. They have access to physicians

who have the ability to develop a protocol for them, and are willing and able to implement it. This is not the case for most women with breast cancer.

The off-trial process involves a great deal of time and expense for clinicians, regulators and investigators, with very little chance of any benefit to the patient, and no chance that we will learn anything that can help other breast cancer patients. Resources devoted to fighting breast cancer should be allocated fairly, based on the best evidence available.

A Fair Policy

NBCC believes that public policy should discourage access to investigational interventions outside of clinical trials. But there are a few circumstances in which it would be fair and appropriate to implement an expanded access protocol.

A breast cancer patient with no treatment options left should have access to a new intervention through an expanded access protocol if 1) the therapy has shown some effectiveness and a low risk of serious harm in a phase II trial and 2) she is not eligible for any open clinical trial investigating the therapy in question.

Single patient INDs should not be granted. Instead, off-trial access should be in the context of expanded access protocols in which distribution of the investigational therapy is fairly and blindly allocated, and data is captured that will add to the scientific knowledge about the intervention. To capture meaningful information, *all* individuals who apply to the program must be followed, and that data must be reported to the trial sponsor.

Conclusion

NBCC recognizes that this is an extremely complex and emotional issue. We all want to help each and every breast cancer patient. NBCC is committed to a public policy agenda that will help *all* women with breast cancer and those at risk. Access to investigational drugs outside of clinical trials must be carefully designed to be fair and to protect the research process that we depend on to bring us closer to eradicating breast cancer.

References

¹ Evidence-Based Medicine has been defined as "the conscientious, explicit and judicious use of current best evidence in making clinical decisions about the care of individual patients." Sackett D et al. Evidence-Based Medicine: What it is and what it isn't. *British Medical Journal* 1996;312:71-2.

² Final Rules for Expanded Access to Investigational Drugs for Treatment Use and Charging for Investigational Drugs. U.S. Food and Drug Administration. 8/13/2009. www.fda.gov

³ See NBCC's position statement on High-Dose Chemotherapy with Bone Marrow Transplant for more information.

⁴ Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; 344(11):783-92.