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findings brief

Evaluating Promising New Treatments for Life-Threatening Disease: Implications of the HDC/ABMT Experience for Treating Breast Cancer

“Enthusiasm for the new treatment led to ‘jumping the gun’ by physicians and patients in the case of HDC/ABMT”

— Richard Rettig,
RAND

Promising new medical treatments for life-threatening diseases often inspire hope, patient demand, and physician enthusiasm before evaluation. In the late 1980s, high-dose chemotherapy/autologous bone marrow transplantation (HDC/ABMT) emerged as a promising medical procedure for treating metastatic and high-risk breast cancer. But procedures, unlike new drugs, face no requirement for evaluation by randomized clinical trials (RCTs). In the early 1990s, HDC/ABMT began diffusing rapidly and widely into clinical practice concurrent with much slower evaluation by RCTs. By the decade’s end, four trials reported “no benefit” to the experimental procedure compared to standard treatment. Two trials reporting positive benefit, when audited, were found to be fraudulent.

Four researchers—Richard Rettig, Ph.D. (RAND); Peter D. Jacobson, J.D., M.P.H. (University of Michigan); Cynthia M. Farquhar, M.D. (University of Auckland, New Zealand); and Wade M. Aubry, M.D. (University of California San Francisco and the Health Technology Center)—combined resources to examine how and why

HDC/ABMT for treating breast cancer diffused widely before its effectiveness was established, how and why technology assessments failed to slow diffusion, and how and why RCTs were finally completed and decisively stopped diffusion. They then drew policy lessons for the evaluation of future similar technologies. In the process, they considered the legal, economic, and political factors that influenced these events.

The researchers found, first, that initial conditions matter; that is, decisions reached at the front-end of the diffusion process drive subsequent developments for a long period of time. “Enthusiasm for the new treatment led to ‘jumping the gun’ by physicians and patients in the case of HDC/ABMT,” says Rettig.

Second, conflicting values occur throughout the entire diffusion and evaluation process. The HDC/ABMT case pitted the demands of women with breast cancer for access to an experimental treatment against the need to evaluate the procedure for effectiveness. According to Rettig, absent a requirement of a randomized clinical trial (RCT), the policy



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issue for this and other procedures is how to manage this basic conflict between access and evaluation. “Patient demands for early access to an experimental therapy, especially by individuals with a life-threatening illness for whom existing therapy is inadequate, must be balanced with society’s need to evaluate a procedure’s effectiveness and protect the integrity of the evaluation process,” says Rettig.

Third, an institutional deficit exists regarding the evaluation of new medical procedures, especially those that are potentially life-saving but very expensive. Formal evaluation of HDC/ABMT by RCTs emerged from a poorly structured relationship between clinical researchers, treating physicians, insurers, and the National Cancer Institute. That relationship was overwhelmed by the “default system” of patients, physicians, patient advocates, lawyers, entrepreneurs, federal administrators, state legislators, and the media. To remedy this deficit, the researchers recommend a public-private partnership involving the National Institutes of Health, clinical scientists, insurers, and patient representatives to oversee the evaluation of medical procedures as they move from small, single-site, hypothesis-generating Phase 2 studies to large, multi-site, hypothesis-testing Phase 3 randomized clinical trials.

Background

For diseases such as breast cancer, a tension frequently exists between the desire of patients and physicians to have access to potentially beneficial treatments as soon as possible and the often lengthy requirements of RCTs. While some oncologists insisted on RCTs as essential to evaluating HDC/ABMT, others advocated wider clinical use on the basis of early studies involving single sites, small numbers of patients, and few or no controls.

Because of the demand for this unevaluated treatment, rapid and widespread clinical use occurred concurrent with slower evaluation. In the 1990s, third-party payers, faced with an investigational treatment that was both expensive and lacked data supporting effectiveness, typically denied coverage. Patients sought redress in litigation. Entrepreneurs exploited financial opportunity. Mandates by the Federal Employees Health Benefits Program and state legislatures required

insurers to cover HDC/ABMT. Technology assessments concluding no evidence of benefit and some potential harm failed to slow diffusion.

In 1999, however, when four clinical trials reported “no benefit” to HDC/ABMT, the treatment’s use plummeted. The only two trials reporting benefit, when audited the following year, were shown to be fraudulent. Unfortunately, between 1989 and 2002, an estimated 23,000 to 40,000 women had already received this expensive and dangerous treatment. Perhaps 1,000 women received the procedure through participation in RCTs.

Methods

The researchers used a number of methodologies and data sources to examine the HDC/ABMT experience. First, the interdisciplinary team of a social scientist, lawyer, and two physicians brought a broader perspective to the analysis than could a single analyst. They held semi-structured interviews with key actors, conducted extensive reviews of published and unpublished scientific literature, analyzed all published court decisions, used data on utilization from the Health Care Utilization Project and the Autologous Blood and Marrow Transplantation Registry, and augmented this with analysis of the print and electronic media.

Results

The researchers found that three major factors drove HDC/ABMT along these parallel paths of widespread clinical use and slow accrual of patients to RCTs. These included the initial conditions, conflicting values, and the absence of an authoritative body to oversee the evaluation of new medical procedures.

Initial Conditions are Critical

The initial conditions surrounding HDC/ABMT that dominated the 1988–1992 period were: 1) a promising procedure for treating breast cancer; 2) no regulatory entity to require its thorough evaluation; and 3) legitimization of its wider use before evaluation by the medical profession. Diffusion was driven by a “default system” of decision making—demands of desperate patients, advice of treating physicians, reaction to insurance coverage denials, litigation, entrepreneurial oncology, federal and state mandates, and the media.

“Analysis of the judicial trials of HDC/ABMT, for example, demonstrates the tensions that exist between these interested parties,” says Rettig. “They show that the judicial forum tends to favor individual patients, not populations of patients, and that judicial bias favors providing access to the experimental and discounting of no evidence of effectiveness.” In spite of these findings, however, results of court cases were mixed, often because of the individual circumstances of contract language interpretation.

Conflicting Values

Conflicting values characterized all parties to the HDC/ABMT story and all stages of the clinical use and clinical evaluation pathways. The basic conflict pitted patient and physician demand for early access to an experimental treatment against a societal need to evaluate the treatment. This conflict was often interpreted as managed care seeking to control costs at the expense of women. The plight of individual patients made great copy, evidenced by innumerable stories focused on conflicts with insurers. But these and other tensions revealed in the HDC/ABMT experience demonstrate in the researchers’ view the need for a mediating institution to manage the conflicting values surrounding the evaluation of new medical procedures.

An Institutional Deficit Exists

Unlike the evaluation of new drugs, society needs a more systematic way to manage the evaluation of unregulated new medical procedures or treatments, especially when patient demand is intense and the interventions are expensive. Rettig and colleagues recommend creation of a public-private partnership that includes the relevant institute of the National Institutes of Health, clinical researchers, health insurers, and patients. This new entity would oversee the transition of expensive but promising investigational treatments from hypothesis-generating Phase 2 studies to publicly funded, hypothesis-testing RCTs.

As conceptualized by the researchers, this group would generate an authoritative statement for patients, physicians and the public about the findings of early studies

and the rationale for conducting an RCT. In return for financing patient care costs of clinical trials, insurers would be provided with protection against denial of coverage outside of trials. Finally, this partnership would change the dynamic at the front end of the evaluation process by establishing a benchmark of clinical knowledge, thus limiting the influence of the decentralized “default system” of lawyers and courts, entrepreneurs, legislatures, and the media.

Implications for the Use of Future Technologies

The team’s findings demonstrate the complex dynamics surrounding the introduction of new treatments for life-threatening conditions before adequate evaluation. The conflicting values make clear that no simple solutions exist to resolving the basic conflict between access and evaluation. Such an entity, they believe, will yield information about clinical effectiveness much faster than current arrangements.

“This case study allowed us to draw lessons useful to policymakers for evaluating similar technologies that will emerge in the future,” says Rettig, “especially medical procedures for treating life-threatening or severely disabling illnesses without good alternatives that may escape evaluation by randomized clinical trials.” He hopes the examination of the HDC/ABMT experience and the lessons learned from it can provide guidance as future technologies come to the fore.

Related Resource

False Hope vs. Evidence-Based Medicine: Bone Marrow Transplantation and Breast Cancer will be published by Oxford University Press in 2005.

For more information, contact Richard A. Rettig, Ph.D., at 703.413.1100, ext. 5299.

About the Author

Susan Edwards is a research assistant working primarily on the HCFO program. She can be reached at 202.292.6700, or susan.edwards@academyhealth.org.