

On the Toxicity of Chemotherapy for Breast Cancer-the Need for Vigilance

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A study published in The Journal of the National Cancer Institute, found that advanced chemotherapy put patients at far greater risks of harm than adverse effect reports from clinical trial data reveal.

"Researchers mined insurance claims for 3,526 women who had intravenous chemotherapy for breast cancer and tallied problems serious enough to require emergency care or a hospital stay."
They found: "Overall, 16% of women in the new study had at least one of eight side effects that required emergency care or hospitalization. Side effects also included blood clots, dehydration, nausea and diarrhea."

An editorial in the same journal issue immediately caught our attention since the authors, Dr. John K. Erban and Dr. Joseph Lau, begin with an affirmation of the Hippocratic Oath.

"Perhaps the most important message is not specific to chemotherapy at all, but instead is a warning that as we enter the new era of targeted therapies, we must be especially vigilant for the potential of late adverse effects."

The problem with clinical trials:

"Despite its low sensitivity in detecting harms, the randomized controlled trial design remains an important source of safety information because it has the potential to provide the most reliable evidence of relative harms if the events are relatively frequent and if the study is properly designed to capture these events. The poor reporting of harms data in clinical trials is a widespread problem in many areas, including oncology. The need for standards of reporting of clinical trials harms data is well recognized, and such standards have been proposed. Effort should be directed at establishing standards of reporting and collection of this information from future breast cancer clinical trials."

The sobering informed acknowledgement is as follows:

"Breast cancer treatment recommendations derive largely from population-based studies. Because the survival benefit of a few percentage points estimated by these studies may be offset by acute, chronic, and late-onset toxicities, it is important to be aware that events such as heart attacks and hip fractures may not emerge for years or even decades after treatment. The inability of our well-designed studies to detect uncommon (less than one in 1000) acute yet important, or even fatal, adverse effects serves as a reminder that clinical trials data are only an estimate of the worth of a drug and that healthy skepticism and diligent reporting of potential toxicities should continue even after an agent enters general use."

The editorial authors then cite a provocative question raised in a 1983 article--"If nothing goes wrong, is everything all right? Interpreting zero numerators."

Clinical trials are simply not designed to detect the wrongs that occur long after the trial termination.

Thus, their conclusion is: "In the case of cancer therapeutics and toxicity data reporting, the answer must be a qualified "no."

How then, do FDA officials justify their most recent data analysis of antidepressants and emergent suicidal behavior in clinical trials?

These officials eliminated from their analysis the rock bottom minimal time frame during which such life-threatening adverse effects occurred.

Stay tuned for further details.

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<http://www.latimes.com/features/printedition/health/la-he-chemotherapy21aug21,1,2440078.story?coll=la-headlines-pe-health>

From Reuters

Chemo may exact a greater toll

In a study of breast cancer patients, the side effects are more serious than earlier thought.

August 21, 2006

Chemotherapy drugs may cause more serious side effects for breast cancer patients younger than 64 than once thought, according to a study released last week.

Researchers mined insurance claims for 3,526 women who had intravenous chemotherapy for breast cancer and tallied problems serious enough to require emergency care or a hospital stay. Their review found more than 8% of women underwent treatment for a fever or infection compared with less than 2% reported in an earlier review of clinical trials.

Other problems also occurred more frequently than previously estimated, according to the study, which was conducted by researchers at Harvard Medical School and the Dana-Farber Cancer Institute.

For example, 5.5% of women were reported to have low blood counts that could raise the risk of infection or bleeding, the study showed. The rates were less than 1% or 2% in clinical trials.

Overall, 16% of women in the new study had at least one of eight side effects that required emergency care or hospitalization. Side effects also included blood clots, dehydration, nausea and diarrhea. All of the women were 63 or younger.

Researchers did not see any evidence that the side effects shortened lifespan, said lead author Dr. Michael Hassett, a researcher at Dana-Farber's Center for Outcomes and Policy Research.

But the findings could help women individually weigh risks versus chances of benefit. Not all women are helped by adding chemotherapy to surgery and other measures.

"Our results don't change the benefits of chemotherapy. We still think chemo can improve survival" for many women, Hassett said.

The women in the new study were treated with various intravenous drugs in families known as alkylating agents, anthracyclines, taxanes and anti-metabolites. The information came from insurance claims filed between 1998 and 2002, before some newer drugs were available.

Chemotherapy's side effects can be minimized through steps such as prescribing blood-cell-boosting drugs or nutritional supplements, said Dr. Edgar Staren, chief medical officer at Cancer Treatment Centers of America. "It's important we make sure [patients] know the various options available."

The study (Hassett M ,O'Malley A ,Pakes J,Newhouse J,Earle C;) Frequency and Cost of Chemotherapy-Related Serious Adverse Effects in a Population Sample of Women With Breast Cancer, was funded by the Agency for Healthcare Research and Quality, and published in the Journal of the National Cancer Institute.

<http://jncicancerspectrum.oxfordjournals.org/cgi/content/abstract/jnci;98/16/1108>

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EDITORIAL

On the Toxicity of Chemotherapy for Breast Cancer-the Need for Vigilance

John K. Erban, Joseph Lau

Primum non nocere, "First, do no harm" is a central tenet guiding medical practice. To know whether a prescribed treatment may cause harm and to assess that quality that has been referred to by the National Surgical Adjuvant Breast and Bowel Project and others as the "worth" of a treatment, clinicians depend on well-designed clinical trials. The function of such trials should be to estimate worth by carefully weighing the difference between the potential benefit and the potential harm of a treatment. However, clinical trials in cancer are usually powered to assess endpoints such as disease-free and overall survival, rather than the toxicities of interventions. Thus, trial design often precludes precise quantification of infrequent toxicities. Furthermore, even in well-designed trials, toxicity reporting is often incomplete, uncertain, or truncated at the reporting of the primary endpoint.

The article by Hassett and colleagues (1 <<http://jncicancerspectrum.oxfordjournals.org/cgi/content/full/jnci;98/16/1096#BIB1>>) in this issue of the JNCI describes an important effort to understand whether toxicity data reported in clinical trials of chemotherapy for breast cancer therapy reflect the experiences of relatively young women (≤ 63 years of age) in the general population who undergo similar treatment. The authors used medical claims and diagnostic codes to determine the frequencies of various toxicities attributable to breast cancer chemotherapy and compared the frequencies of these toxicities in a chemotherapy-treated cohort with those in a propensity score-adjusted cohort of breast cancer patients who did not receive chemotherapy. Imbalances that might have influenced the frequency of toxic events were adjusted to the extent possible, but small differences remained between the two groups. The frequencies in the treated and untreated cohorts of toxicities that are not traditionally associated with chemotherapy such as fractures, asthma, kidney disease, back pain, and thyroid disorders were also compared.

Not surprisingly, the frequency of chemotherapy-related toxicities was greater among chemotherapy recipients, but there was no difference in the frequency of nonrelated toxicities between recipients and nonrecipients. Increased toxicities in chemotherapy recipients entailed substantial incremental costs for this group of patients and considerable additional cost per affected person. Several toxicities appeared to be substantially more frequent than what was reported previously in randomized controlled trials (2). Adding to the importance of this study is the fact that it is the first to assess toxicities in a younger population of breast cancer patients. Younger patients are frequently offered chemotherapy in the adjuvant setting, and though improvements in survival may be below 5%, women will often accept chemotherapy for as little as a 1%-2% survival advantage (3).

The conclusions about the frequency and cost of chemotherapy-related toxicities are important and intriguing, but the methodology used deserves comment. First, the raw data were derived from employer-provided health insurance claims and coding information; other sources or direct observation were not used. Thus, certain socioeconomic groups are likely to have been excluded outright, and the racial distribution was unknown and unlikely to represent the population as a whole. Underrepresentation of certain populations has also been shown to exist within NCI-sponsored trials (4), and this study does not address this particular question either. The authors do not comment on the question of whether toxicity incidence and reporting may differ among ethnic groups. Second, due to the imbalance between the groups that did or did not receive chemotherapy, equalization by generation of a propensity score model was required, and the validity of this model is

key to the reliability of the conclusions. Importantly, the authors compared the data generated by including only those chemotherapy patients for whom matched controls were available with data generated by including all chemotherapy patients and found no differences.

Regardless of these methodologic issues, this study found a much higher frequency of chemotherapy-related toxicities than did NCI-sponsored and other well-conducted randomized controlled trials. For this reason, there are several important messages implicit in this article. One is the need to continue to develop patient-specific predictive instruments (5) to focus the use of therapeutic drugs and the supportive treatments that accompany the drug therapies. As therapy becomes increasingly tailored to individuals, population-based recommendations will become less widely used, and thus, the potential for indiscriminate toxicity will be reduced. Another important message is that trial data are only approximations of risk that may underestimate the true likelihood of an adverse event.

Perhaps the most important message is not specific to chemotherapy at all, but instead is a warning that as we enter the new era of targeted therapies, we must be especially vigilant for the potential of late adverse effects. Newer molecular therapeutics are increasingly effective against breast cancer and less toxic in the short term. Thus, the medical barriers to their use are coming down. The experience with trastuzumab and aromatase inhibitors, drugs that are important in the adjuvant setting to prevent breast cancer recurrence, illustrates these trends. As new drugs of increasing efficacy and few acute toxicities emerge, the tendency will be to push them to market, and there will be few incentives for longer term toxicity studies. After all, the primary endpoints in trials will continue to be disease-free and overall survival in the shorter term. Without careful long-term tracking of late adverse effects, there is a risk that very important toxicity events will occur unnoticed. Moreover, current trial design is incapable of assessing the toxicities that may occur from rapid sequential use of novel agents.

Some in the medical community have already pointed out the potential for long-term toxicities posed by novel therapeutics. For example, in an editorial accompanying an article recently published in the *New England Journal of Medicine* comparing letrozole to tamoxifen for adjuvant treatment of hormone receptor-positive breast cancer, Swain emphasizes the need to continue to be observant for any potential cardiac differences that may emerge with time (6). For young survivors of breast cancer, cardiovascular events and bone health are two important areas in which meticulous tracking of long-term toxicity of new drugs in ongoing trials is necessary if we are to know how to advise practitioners and patients on best practices for the future.

Despite its low sensitivity in detecting harms, the randomized controlled trial design remains an important source of safety information because it has the potential to provide the most reliable evidence of relative harms if the events are relatively frequent and if the study is properly designed to capture these events. The poor reporting of harms data in clinical trials is a widespread problem in many areas, including oncology. The need for standards of reporting of clinical trials harms data is well recognized, and such standards have been proposed (8). Effort should be directed at establishing standards of reporting and collection of this information from future breast cancer clinical trials (7).

Breast cancer treatment recommendations derive largely from population-based studies. Because the survival benefit of a few percentage points estimated by these studies may be offset by acute, chronic, and late-onset toxicities, it is important to be aware that events such as heart attacks and hip fractures may not emerge for years or even decades after treatment. The inability of our well-designed studies to detect uncommon (less than one in 1000) acute yet important, or even fatal, adverse effects (9) serves as a reminder that clinical trials data are only an estimate of

the worth of a drug and that healthy skepticism and diligent reporting of potential toxicities should continue even after an agent enters general use. Thus, it is useful to remember the provocative question raised by Hanley and Lippman-Hand with the title of their 1983 article "If nothing goes wrong, is everything all right? Interpreting zero numerators" (10) In the case of cancer therapeutics and toxicity data reporting, the answer must be a qualified "no."

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