Increasing Statistical Power in Breast Cancer Clinical Trials

25TH ANNUAL
SAN ANTONIO BREAST CANCER SYMPOSIUM

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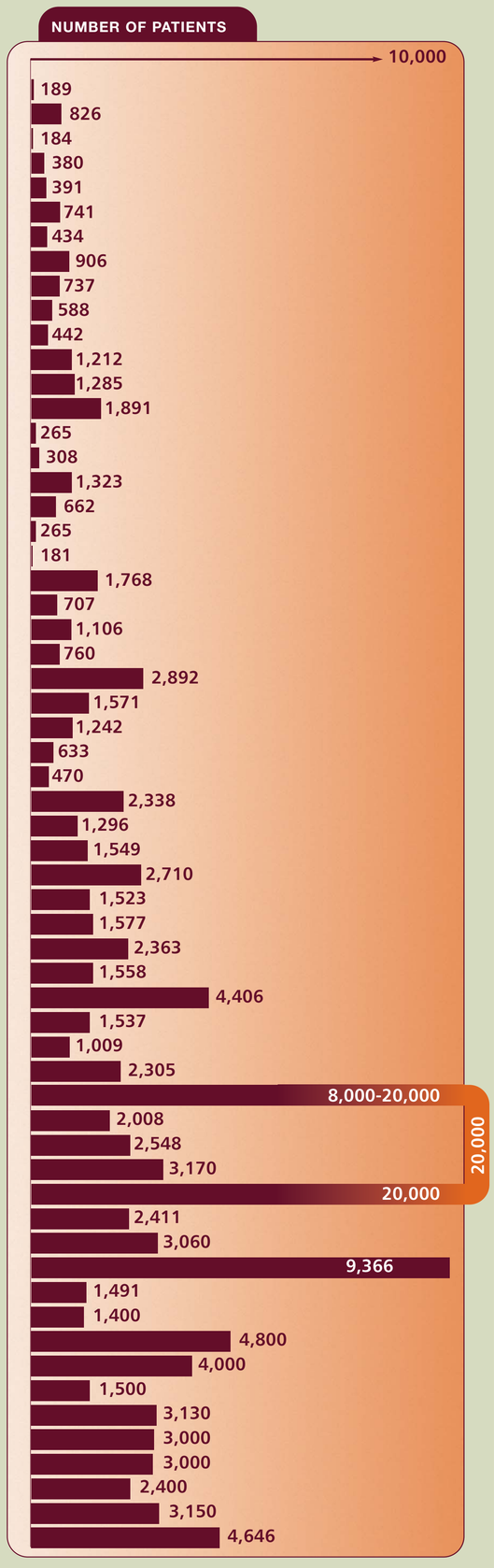
The recently reported decline in breast cancer mortality in the United States and United Kingdom has been attributed to multiple factors, including the increased use of screening mammography, adjuvant chemotherapy and endocrine therapy with tamoxifen. These advances are directly attributable to practice standards that have been shaped by data from randomized clinical trials. The human impact of these reductions in breast cancer mortality has led to larger cooperative studies with the statistical power to detect modest, but important, improvements in outcomes. A fascinating footnote is the recently reported ATAC adjuvant trial that has about 10 times as many patients as initial adjuvant studies launched in the 1970s.

SELECT KEY RANDOMIZED TRIALS 0F ADJUVANT SYSTEMIC THERAPY IN EARLY BREAST CANCER

			NUMBER OF PATIENTS
1948	Christie	Ovarian ablation v C	189
1958	NSABP B-01	Thiotepa v P	826
1961	NSABP B-03	Ovarian ablation v C	184
1972	NSABP B-05	L-PAM v P	380
1973	INT Milan-7205	12 CMF v C	391
1975	NSABP B-07	L-PAM 6mg v L-PAM 4mg+5-FU	741
1975	INT Milan-7502	12 v 6 CMF	434
1975	CALGB 7581	CMFVPr v CMF v CMF+MER	906
1976	NSABP B-08	L-PAM+5-FU v L-PAM+5-FU+MTX	737
1976	Christie	TAM v C	588
1976	Stockholm B 76G1-2	TAM+XRT v TAM+CMF v XRT v CMF	442
1977	Danish 77b pre	12C v 12CMF v Levam v C	1,212
1977	NATO	TAM v C	1,285
1977	NSABP B-09	L-PAM+5-FU v L-PAM+5-FU+TAM	1,891
1977	NSABP B-10	L-PAM+5-FU v L-PAM+5-FU+C.parvum	265
1978	GUN Naples	TAM v C	308
1978	Scottish	TAM v TAM > recurrence	1,323
1978	ECOG 5177	CMF v CMFPr v CMFPr+TAM	662
1978	ECOG 6177	CMFPr v CMFPr+TAM v C	265
1978	ECOG 1178 post	TAM v P	181
1980	CRC 2	TAM v CTX v TAM+CTX v C	1,768
1981	NSABP B-11	L-PAM+5-FU v L-PAM+5-FU+DOX	707
1981	NSABP B-12	L-PAM+5-FU+TAM ± DOX	1,106
1981	NSABP B-13	MTX→5-FU+LV v C	760
1982	NSABP B-14	TAM v P	2,892
1982	Danish 82b pre	CMF v CMF+XRT	1,571
1982	Danish 82c post	TAM v TAM+XRT	1,242
1982	ECOG 4181 post	TAM 5 v 1 year	633
1982	ECOG 5181 pre	TAM 5 v 1 year	470
1984	NSABP B-15	AC v AC+3CMF v 6CMF (+R)	2,338
1984	NSABP B-16	TAM v L-PAM+5-FU+A+TAM v 3AC+TAM	1,296
1985	CALGB 8541	CAF(High/Low/Standard)→XRT or TAM	1,549
1987	ZIPP	GOS v TAM v GOS+TAM v C	2,710
1988	NSABP B-18	S→AC v AC→S	1,523
1988	NSABP B-19	M→F+LV v CMF	1,577
1988	NSABP B-20	TAM v M→F+TAM v CMF+TAM	2,363
1989	SWOG 8814/INT 0100	TAM v FAC + concur or seq TAM	1,558
1989	SWOG 8897/INT 0102	CMF v CAF v CMF→TAM	4,406
1989	ECOG 5188/INT 0101	FAC v FAC+GOS v FAC+GOS+TAM	1,537
1989	NSABP B-21	XRT+P v XRT+TAM v TAM	1,009
1989	NSABP B-22	AC v A+CTX intensified v AC intensified	2,305
1991	aTTom	TAM x 5 more years v Stop Tam after 2 years	8,000-20,000
1991	NSABP B-23	CMF+TAM v CMF+P v AC+TAM v AC+P	2,008
1992	NSABP B-25	[AC (1200 x4 v 2400x2 v 2400x4)]+G-CSF	2,548
1993	CALGB 9344/INT 0148	CA(60/75/90)→ T v C	3,170
1995	ATLAS	Tam x 5 more years v Stop Tam	20,000
1995	NSABP B-27	AC→S v AC→T→S v AC→S→T	2,411
1995	NSABP B-28	AC+TAM v AC+TAM→T	3,060
1996	ATAC	Anastrozole v TAM v Anastrozole + TAM	9,366
1997	BCIRG-001	TAC v FAC	1,491
1997	CALGB 9741	Seq v Comb [ACT v ACT+G-CSF]	1,400
1998	CALGB 49805	Letrozole v P	4,800
1999	NSABP B-30	AC→T v AT v ACT	4,000
2000	CAN-NCIC-MA21	FEC v EF/G-CSF T v AC→T	1,500
2000	BCIRG-005	TAC v AC→T	3,130
2000	NCCTG-N9831	AC→T v AC→T→H v AC→TH→H	3,000
2001	NSABP B-33	Exemestane v P	3,000
2001	NSABP B-34	Clodronate v P	2,400
2001	BCIRG-006	AC→T v AC→TH v TCH	3,150
2002	CALGB 40101	AC x 4 v AC x 6 v T x 12 v T x 18	4,646



C = Control P = Placebo S = Surgery T = Taxane

HISTORICAL PERSPECTIVE

"Arguably one of the most important advances during the last 50 years has been the introduction of prospectively randomized controlled trials to clinical medicine. Such trials provide information about the natural history of a disease and evaluate the worth of a particular therapy. Moreover, they allow for testing of biological hypotheses and, thus, provide a mechanism whereby the scientific method can be applied to clinical problem-solving. By replacing anecdotal information (which has influenced therapeutic decision-making in the past) with more credible and substantive data, clinical trials play a major role in transforming the practice of medicine from an art to a science. As a vital component of the "research chain," clinical trials are an essential link between the laboratory and the clinic, providing means for determining whether the use of laboratory findings in the treatment of patients is justified. Without trials, much of the scientific information currently being reported could not be evaluated for its therapeutic worth."

—Bernard Fisher, MD
News from the Commission on Cancer of the American College of Surgeons 1991;2(2).

TRIALS AND CLINICAL DECISIONS

"The randomised controlled trial has become the gold standard for evidence-based medicine; through the unbiased comparison of competing treatments it is possible to accurately quantify the cost-benefits and harm of individual treatments. This allows clinicians to offer patients an informed choice and provides the data on which purchasing authorities can make financial decisions. We, of course, subscribe to this view but also recognize this as a gross over-simplification of the power of the randomised controlled trial. The randomised controlled trial is the expression of deductive science in clinical medicine. Not only is it the most powerful tool we have for subjecting therapeutic hypotheses to the hazard of refutation, but also the biological fallout from such trials should allow clinical scientists to refine biological hypotheses. Trials of treatments for breast cancer have, at least twice, contributed substantially to a paradigm shift in our understanding of the disease."

—Michael Baum, ChM, FRCS; Joan Houghton, BSc
Br Med J 1999;319:568-571.

INTERNATIONAL META-ANALYSIS

There are thousands of randomized trials in the world, which will lead to "zigs and zags" in the data. And, the "zags" are probably the ones that are going to be the most noteworthy and the most emphasized in meetings, because they look odd. So if you take lots of trials and then pick out the ones where the results look out of line with the other ones, then you're quite likely to have something that is misleading. You've got to systematically bring together all the evidence in the world — look at it irrespective of what the individual study shows — see what the grand total looks like, and then you've got something reliable. We've seen too many trial results that prove to be evanescent. But if you put all of the trials together, you get reliable knowledge. If you don't, you don't.

—Richard Peto, FRS

SELECT PUBLICATIONS

Collins R et al. **Avoidance of large biases and large random errors in the assessment of moderate treatment effects: The need for systematic overviews.** *Stat Med* 1987;6:245-250.

Ellis PM et al. **Randomized clinical trials in oncology: Understanding and attitudes predict willingness to participate.** *J Clin Oncol* 2001;19:3554-3561.

Giuliano AR et al. **Participation of minorities in cancer research: The influence of structural, cultural and linguistic factors.** *Ann Epidemiol* 2000;10(8 Suppl):S22-34.

Hutchins LF et al. **Underrepresentation of patients 65 years of age or older in cancer-treatment trials.** *N Engl J Med* 1999;341:2061-7.

Lara PN et al. **Prospective evaluation of cancer clinical trial accrual patterns: Identifying potential barriers to enrollment.** *J Clin Oncol* 2001;19:1728-1733.

Siminoff LA et al. **Factors that predict the referral of breast cancer patients onto clinical trials by their surgeons and medical oncologists.** *J Clin Oncol* 2000;18:1203-1211.