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EFFECTS OF ADJUVANT TAMOXIFEN AND OF CYTOTOXIC THERAPY ON MORTALITY IN EARLY BREAST CANCER

An Overview of 61 Randomized Trials among 28,896 Women

EARLY BREAST CANCER TRIALISTS' COLLABORATIVE GROUP

Abstract We sought information worldwide on mortality according to assigned treatment in all randomized trials that began before 1985 of adjuvant tamoxifen or cytotoxic therapy for early breast cancer (with or without regional lymph-node involvement). Coverage was reasonably complete for most countries. In 28 trials of tamoxifen nearly 4000 of 16,513 women had died, and in 40 chemotherapy trials slightly more than 4000 of 13,442 women had died. The 8106 deaths were approximately evenly distributed over years 1, 2, 3, 4, and 5+ of follow-up, with little useful information beyond year 5.

Systematic overviews of the results of these trials demonstrated reductions in mortality due to treatment that were significant when tamoxifen was compared with no tamoxifen ($P<0.0001$), any chemotherapy with no chemotherapy ($P = 0.003$), and polychemotherapy with single-agent chemotherapy ($P = 0.001$). In tamoxifen trials, there was a clear reduction in mortality only among women 50 or older, for whom assignment to tamoxifen reduced the annual odds of death during the first five years by about one fifth. In chemotherapy trials there was a clear reduction only among women under 50, for whom assignment to polychemotherapy reduced the annual odds of death during the first five years by about one quarter. Direct comparisons showed that combination chemotherapy was significantly more effective than single-agent therapy, but suggested that administration of chemotherapy for 8 to 24 months may offer no survival advantage over administration of the same chemotherapy for 4 to 6 months.

Because it involved several thousand women, this overview was able to demonstrate particularly clearly that both tamoxifen and cytotoxic therapy can reduce five-year mortality. (N Engl J Med 1988; 319:1681-92.)

IN early breast cancer, all clinically apparent disease can, by definition, be removed surgically. After such surgery (with or without radiotherapy), adjuvant systemic treatments may be considered. The two most widely tested types of adjuvant therapy are tamoxifen, an antiestrogen generally taken for one or more years, and various cytotoxic drugs, given singly or in combination for at least a few months. Many randomized trials of these two types of adjuvant treatment have been undertaken, and the purpose of the present report is to provide an overview of the mortality results in those trials. A more extensive report[1] includes summaries of individual trials, additional details on methods and mortality, data on recurrence, and overviews of other types of trials.

Breast cancer is a common condition in many parts of the world. If some widely practicable treatment could be reliably shown to produce even a moderate decrease in early mortality (e.g., reducing mortality from 25 percent to 20 percent within the first few years), death due to breast cancer could be avoided or appreciably delayed in many thousands of women each year. Hence, it is important to be able to distinguish reliably between a treatment that produces a moderate effect on mortality and one that produces little or no effect. If such differences in mortality are to be assessed reliably, both moderate random errors and moderate biases must be avoided. Systematic overviews of all relevant randomized trials can help in both respects.[2,3] First, since far more patients are involved in an overview than in a single trial, the stand-

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ard deviation of any apparent reduction in mortality is far smaller in an overview than in any individual trial contributing to the overview. Second, if many trials address related questions, then by chance alone some are likely to appear misleadingly promising while others appear misleadingly unpromising. Emphasis on just the more promising (or just the less promising) trial results could introduce biases into the assessment of treatment. Similarly, even if all available trial results are considered together, undue emphasis on subgroups of patients (e.g., only those less than 50 years old) among whom the effects of treatment appear particularly promising or unpromising ("data-derived subgroups") may likewise be misleading. These sources of bias can be limited by cautious interpretation of the findings of the overview, with greater emphasis on the overall findings than on the findings in particular subgroups.

METHODS

Collaboration was sought[4] between the coordinators of all unconfounded randomized trials of treatment of early breast cancer in which tamoxifen was compared with no tamoxifen, chemotherapy with no chemotherapy, polychemotherapy with single-agent chemotherapy, or short-term chemotherapy with longer-term use of the same chemotherapy. In "unconfounded trials," one group differs from another only in the treatment of interest; thus, our tamoxifen overview includes trials in which tamoxifen plus chemotherapy was compared with the same chemotherapy alone, but not trials in which tamoxifen plus prednisone was compared with no treatment. In trials of chemotherapy, however, prednisone was considered an integral part of the regimen being evaluated; therefore, trials in which chemotherapy plus prednisone was compared with no treatment were included in the chemotherapy overview. Trials were identified from lists prepared by the Union Internationale Contre le Cancer, the U.S. National Cancer Institute, and the U.K. Coordinating Committee on Cancer Research, from a computer-aided search of the International Cancer Research Data Bank, from abstracts presented at meetings of the American Society of Clinical Oncology, the American Association of Cancer Research, and the Union Internationale Contre le Cancer, from the reference lists of published trials, and from discussions with investigators. Trials were included only if they were believed to have been randomized in a manner that precluded prior knowledge of the next treatment assigned. All patients undergoing randomization were evaluated according to the treatment assigned them, irrespective of whether they actually received it or were "eligible."

Information on the age, nodal status, date of entry, and date of death was sought for each patient. Data sets submitted by each investigator were checked by the statistical office for the internal consistency of individual patient records, for the balance of group sizes overall and according to certain prognostic categories, and for other indicators of possible errors in the conduct of the trial or the submission of data.[3] Queries were referred back to individual investigators for clarification, and the complete set of information on each trial was also referred back for confirmation. Four collaborative groups provided only tabular data, with no information on individual patients. All trials conducted in the Soviet Union and Japan were excluded from the present report because complete data on these trials were not available, but it is anticipated that those studies will be included in subsequent reports. Trials were included only if randomization was begun before January 1, 1985. Neither patients undergoing randomization after August 1985 nor deaths occurring after that date were included.

Information on each trial is being published separately by its coordinators as short appendixes to the full report of this collaboration.[1] Those appendixes provide data on patients according to age (<50 and ≥ 50 years when randomized) and treatment group, giving the numbers of deaths during each year (1, 2, 3, 4, and 5+) after randomization, and the numbers of patients still at risk at the start of each year.

Statistical Analysis

The availability of separate data for each year of follow-up allowed the use of log-rank analyses[5] to estimate the effects of treatment on the annual odds of death. For each trial the total number of deaths "observed" (O) among patients assigned to treatment was compared with the number of deaths "expected" (E) to occur among the survivors at the start of each year if the probability of death was unrelated to treatment. The difference (observed minus expected [O − E]) is negative if the treatment group fared better than the control group, and is equal to approximately half the number of deaths avoided. This is because the expected number reflects an average mortality rate that is about halfway between that in the treatment group and that in the control group. (For example, an O − E of −50 might suggest that about 100 deaths were avoided.) The variance (V) of O − E is calculated according to standard methods (see "Arithmetic Procedures" below). O − E and V can be used for three purposes.

First, they may be used in testing for significance. The square root of V is the standard deviation (SD) of O − E, and the ratio, $z = (O - E)/SD$ — or equivalently, chi-square $= (O - E)^2/V$ — may therefore be used to estimate the P value. Throughout this report, all P values given are two-tailed (e.g., $z = -1.96$ corresponds to $P = 0.05$).

Second, they may be used descriptively. The statistic exp(z/SD) provides a useful estimate of the ratio of the annual odds of death in the treatment group to that in the control group, with a 95 percent confidence interval given approximately by exp(z/SD±1.96/SD). An odds ratio of 0.8 corresponds to a 20 percent reduction (r) in the annual odds of death. The approximate standard deviation of this odds reduction is given by −r/z. The percentage reduction in the odds of death indicates the proportional reduction in mortality produced by treatment. (A further discussion of these estimates, including the decision not to take account of any heterogeneity between the real magnitudes of the treatment effects in different trials, will be given elsewhere.[1]) Approximate chi-square tests for heterogeneity involve subtraction of the chi-square test statistic for an overview from the sum of the chi-square test statistics for each contributing trial.

Third, they may be used to combine information from different trials that have addressed related questions, yielding both a significance test and a description of the combined result. For example, if three trials of a particular treatment yielded O − E values of −7.2, −10.5, and −5.9, with respective variances of 25.1, 35.2, and 10.3, then the sum of the individual O − E values (−23.6) would, if treatment had no effect, have a variance equal to the sum of the individual variances (70.6) and hence a standard deviation of 8.4. Although none of the three trials is clearly significant on its own, the favorable trend in each reinforces the trends in the others, giving a total that is significantly different from zero ($z = -23.6/8.4 = -2.8$; $P<0.01$). These totals may also be used to calculate descriptive statistics (as above). For example, $\exp(-2.8/8.4) = 0.72$ corresponds to a reduction in the annual odds of death of about 28(±10) percent in these trials.

For each trial, the observed odds reduction is plotted in the figures as a black square, with its 99 percent confidence interval as a horizontal line. A diamond shape represents the odds reduction and 95 percent confidence interval for the overview of the individual trials. The variance of O − E for a small trial with only one death might be only 0.2, whereas that for a larger trial with 100 deaths might be greater than 20. In general, the variance of O − E is a useful and precise[2] measure of the amount of statistical "information" provided by a trial. To increase the visual impact of the larger trials, which contribute most data, the areas of the black squares are proportional to these variances.

All calculations of O − E and its variance were retrospectively stratified[5] according to the year of follow-up (1, 2, 3, 4, and 5+) and age (<50 and ≥50). In trials in which treatment-assignment ratios were not constant, a separate stratum was formed whenever the assignment ratios were altered. The survival rates in the treatment and control groups in each year could be estimated from the overall survival rate during that year and from the reduction in the odds of death suggested by the O − E calculations for that year only. Survival curves for the treatment and control groups were calculated by multiplying these annual survival rates together. The difference between the percentages of patients alive at five years indicates the absolute improvement in survival produced by treatment. (The few deaths occurring in patients followed beyond year 5 are included in the category "5+"; open squares or circles are used to indicate that this last period is open-ended.) Because patients were assigned to treatment or control groups in a ratio of 1:1 in almost all the trials, these survival curves were virtually identical to those calculated by standard life-table methods, in which the death rate in a particular year is estimated simply by dividing the total number of deaths by the total number of "woman-years" (i.e., the number of women at risk at the start of that year multiplied by the average period of observation during the year).

To guard against the theoretical possibility that the results might have been seriously biased by more thorough follow-up of the treated patients than the controls, the main analyses were repeated with censoring of all data at January 1, 1984. In practice, this did not produce any substantial change in the results (data not shown).

Arithmetic Procedures

Suppose that a total number (N) of patients under the age of 50 are at risk at the beginning of year 1 of a study, with a fraction (f) assigned to the active-treatment group (and hence 1 − f assigned to the control group), and suppose that during year 1 a total number (D) of these N patients die. If there is no difference in mortality between the treatment and control groups, then the expected number of first-year deaths in the treatment group is given by fD, and its variance by $fD(1 - f)(N - D)/(N - 1)$. Adding the results of one such calculation with different values for f, N, and D for each year (1, 2, 3, 4, and 5+) in women under 50, and of similar calculations in older women, will yield the retrospectively stratified "log-rank" expected number of deaths (E) and its variance (V).[5]

The Trials

Information was available from 61 trials on a total of 28,896 women, 8106 of whom were reported to have died (Table 1). The deaths were approximately evenly distributed over years 1, 2, 3, 4, and 5+ of follow-up, providing useful information for up to about five years but not beyond.

Table 1 summarizes the 28 trials of tamoxifen that were available for review. They studied in total 16,513 women, 3782 of whom were reported to have died. Only one fifth of the patients in the tamoxifen trials were under 50. Of these younger women, most were studied in trials comparing tamoxifen plus chemotherapy with chemotherapy alone, and fewer than one third were studied in trials comparing tamoxifen alone with no other adjuvant therapy. In contrast, two thirds of the women 50 or older were studied in trials of tamoxifen alone (see Results).

Table 1 also summarizes the chemotherapy trials available for review. These involved 13,442 women, 4503 of whom were reported to have died. However, only 9069 of these women, 2872 of whom have died, were entered into trials comparing chemotherapy with no chemotherapy. Since the most extensively studied cytotoxic regimens in these trials involved a combination of cyclophosphamide, methotrexate, and fluorouracil, analyses of trials evaluating this combination (with or without other agents) are presented separately. Trials of chemotherapy used only during the perioperative period (i.e., only in the first few days or weeks after surgery) were not included since the data available for the overview were too limited.

Table 1. Randomized Trials Available for Evaluation of Tamoxifen and Chemotherapy.

	No. of Trials	Patients Known to Be Dead	No. of Patients Randomized
Trials evaluating tamoxifen*			
5 yr tamoxifen vs. no tamoxifen	2	253	1,518
3 yr tamoxifen vs. no tamoxifen	1	56	179
2 yr tamoxifen vs. no tamoxifen	16	2014	9,810
1 yr tamoxifen vs. no tamoxifen	8	1384	4,742
6 mo tamoxifen vs. no tamoxifen	1	75	264
Subtotal, tamoxifen	*28*	*3782*	*16,513*
Trials evaluating prolonged chemotherapy (3–24 mo, excluding "perioperative" treatment)†			
CMF vs. no chemotherapy	11	920	3,380
CMF with other cytotoxic drugs (e.g., CMF then E, CMFV, CMVALeu, CMFVPr) vs. no chemotherapy	5	367	1,467
Other types of polychemotherapy (e.g., CFPr, AC, CVF, MelF, MelV, MelM, MelMF, AC, or LMF) vs. no chemotherapy	11	743	2,315
Single-agent chemotherapy (e.g., Mel, C, F, or M) vs. no chemotherapy	8	971	2,257
Subtotal, chemotherapy	*31‡*	*2872‡*	*9,069‡*
Trials comparing more with less chemotherapy			
Polychemotherapy vs. single-agent	10	1144	3,005
Prolonged vs. less prolonged polychemotherapy	6	752	2,111
Subtotal, all chemotherapy trials	*40‡*	*4503‡*	*13,442‡*
Total, all trials	*61‡*	*8106‡*	*28,896‡*

*About half the patients were assigned to tamoxifen treatment, and half were not.

†For explanation of abbreviations of drug names, see Appendix.

‡Not additive because 2152 patients (573 dead) in three-way trials or in two-by-two trials were counted twice.

In the chemotherapy trials, slightly more than one third of all patients were less than 50 years old.

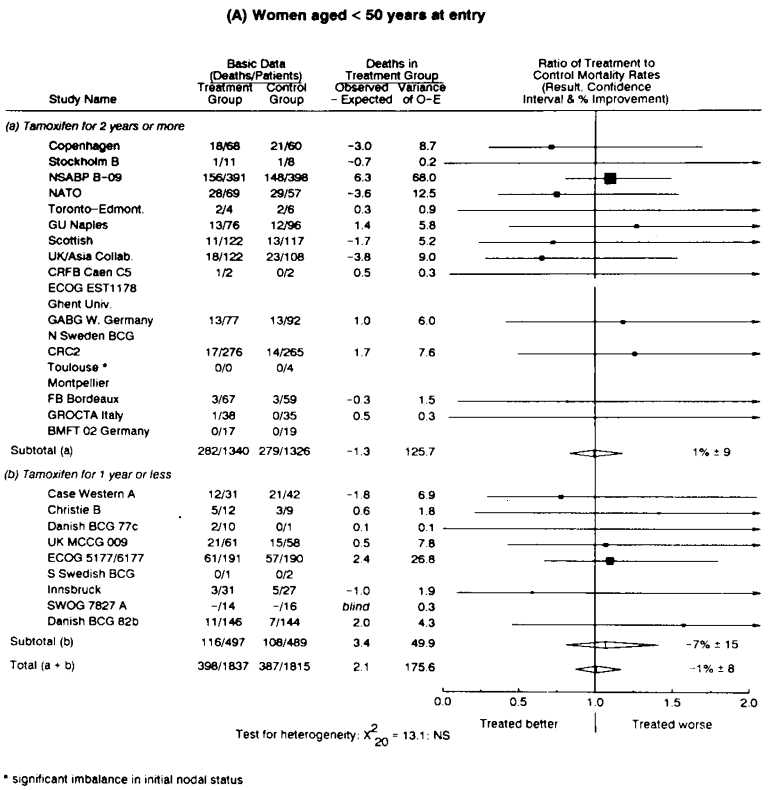
Results

Tamoxifen Trials

A summary of each of the 28 trials involving tamoxifen that were included in the overview, along with an estimate of the effect of tamoxifen in all the trials combined, is shown in Figure 1 according to age group (<50 and ≥50). For each trial, the quantity O − E and its variance are listed separately, and beside these values the ratio of the annual odds of death (with 99 percent confidence interval) in the tamoxifen-assigned group as compared with the control group is shown graphically. There is great variability in the apparent effect of treatment in the individual trials, but the wide confidence intervals reflect the unreliability of these separate estimates.

If tamoxifen had no effect on mortality among the older or the younger patients in any of these 28 trials, each value for O − E could equally well have been positive or negative, and the grand total of these values would have differed only randomly from zero. However, most of the O − E values were negative,

especially those for the older women, and their total was −148.3 (−150.3 for women 50 or over [Fig. 1B], and +2.1 for those under 50 [Fig. 1A]). This suggests that nearly 300 deaths were avoided or delayed by tamoxifen. Summation of the corresponding variances for each O − E value yielded a total variance of 851.3 (675.7 from Fig. 1B plus 175.6 from Fig. 1A), the square root of which (29.2) provides an estimate of the standard deviation of the grand total of the individual O − E values. Dividing the grand total by its standard deviation ($z = -148.3/29.2 = -5.1$; $P<0.00001$) indicates that it is more than 5 SD away from zero. This represents a reduction of 16(±3) percent in the odds of death among women of all ages assigned to tamoxifen treatment and is far too large to be plausibly attributed merely to the play of chance. Unless there is evidence of a large bias in favor of treatment, it must be accepted that adjuvant tamoxifen can delay death. (Only one study is known to have had a large imbalance in prognostic features [Fig. 1], and in it disproportionately more patients with poor prognoses were assigned to tamoxifen. Omission of this trial from the overview would only slightly strengthen the overall findings.)



Heterogeneity of Effects

Although the analyses presented here demonstrate that tamoxifen significantly affects mortality, they provide no reason to suppose that the magnitude of this effect varies from trial to trial because of differences in dosages, schedules of administration, or patient variables. A test for heterogeneity of the apparent effects in the different trials gave a nonsignificant result (chi-square with 27 degrees of freedom = 21.5), but such tests lack power and do not exclude the possibility that some important differences in the effects of treatment do exist. A more sensitive way of identifying such differences involves indirect comparison of trial data grouped according to specific patient variables (e.g., age) or treatment regimens (e.g., duration of treatment).

The data from the trials listed in Figure 1 are grouped by duration of tamoxifen treatment (two or more years or less than two years). Figure 1B shows that among women over 50, in all but two of the trials the patients in the tamoxifen group fared somewhat better than those in the control group: all but two of the black squares in Figure 1B are to the left of the solid vertical line. When the trials are considered separately, however, only one has a 99 percent confidence interval that does not cross the solid vertical line, and hence yields a P value below 0.01. All the other trials yield less extreme P values and thus do not provide clearly significant evidence of benefit. Taken together, however, their generally favorable results reinforce each other. The 95 percent confidence limits for overviews of various subgroups of these trials are shown as diamond-shaped symbols. Reductions in the odds of death are significant in the trials involving tamoxifen treatment for two years or longer (23[±4] percent; $P<0.00001$), in those involving treatment for one year or less (15[±6] percent; $P<0.01$), and in all trials in the overview considered together (12,861 women over 50: 20[±3] percent; $P<0.00001$). The dashed vertical line indicates this overall result — i.e., a 20 percent reduction — and comparison of the lengths of the confidence intervals for the individual trials with the narrowness of the separation between the dashed and the solid vertical lines shows that the individual trials were not large enough to detect a 20 percent difference reliably.

Figure 1A shows the corresponding results in women who were under 50 years of age on entry to the tamoxifen trials. The confidence intervals are longer because the number of patients was smaller (only 3652 women), and hence are less informative than those for the older women — indeed, for the younger women, even the overview of all availa-

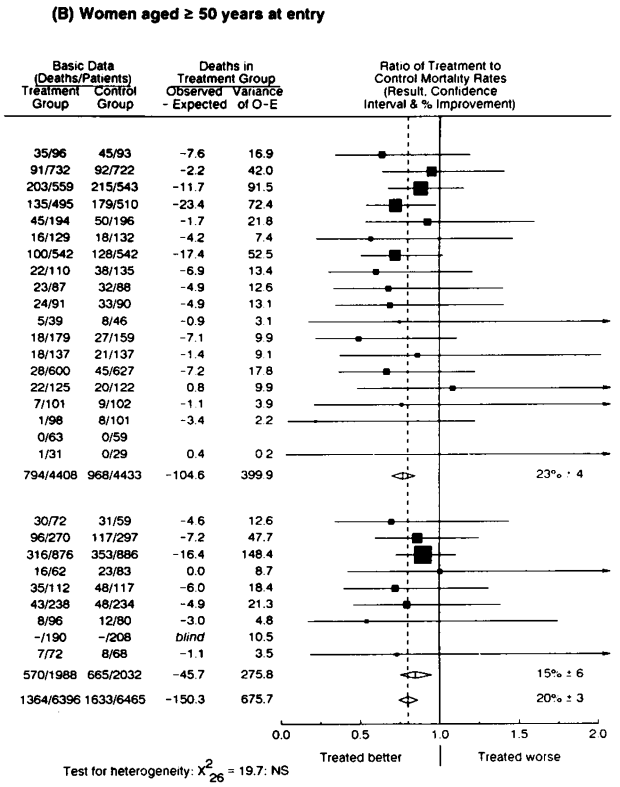


Figure 1. Mortality among Women in All Available Trials Comparing Adjuvant Tamoxifen with No Tamoxifen (Including Trials with Identical Chemotherapy for Both Treatment and Control Groups).

The trials in each category are listed in order of maturity (the oldest first). The statistical calculations of the O − E value and its variance are presented numerically and graphically. The fundamental comparison is of the difference (O − E) between the number of deaths actually observed (O) in the treatment arm of each trial, and the number expected (E) if treatment had no effect (therefore, a negative value for O − E suggests benefit). The ratio of the annual death rate in the treatment group to that in the control group is plotted for each trial (black square), along with its 99 percent confidence interval (horizontal line). The presence of a black square to the left of the solid vertical line suggests benefit (but this benefit is significant at the level of P<0.01 only if the entire confidence interval for that trial is also to the left of the solid vertical line). Overviews of some or all of the trial results (and their 95 percent confidence limits) are represented by diamond-shaped symbols, beside each of which is the reduction in the odds of death (percent ±SD) associated with treatment in those trials. The solid vertical line indicates zero effect, and the dashed vertical line indicates the overall effect (where this differs appreciably from zero). For a list of the trials, see the Appendix.

ble trials (diamond-shaped symbol near the bottom of Fig. 1A) is not as accurate as might be wished. The estimated difference between the effects of tamoxifen in these two age groups is statistically significant (test for interaction = 2.8 SD; P<0.01), but the 95 percent confidence interval for the effect of tamoxifen on mortality in women under 50 is wide, ranging from a 17 percent adverse effect to a 13 percent benefit.

Effects of Treatment According to Year of Follow-up

The approximate effects of tamoxifen in each successive year of follow-up are illustrated by survival curves (Fig. 2). There was little apparent difference in survival between the tamoxifen group and the control group during the first year or two after randomization. Among women under 50 (Fig. 2A), no later difference

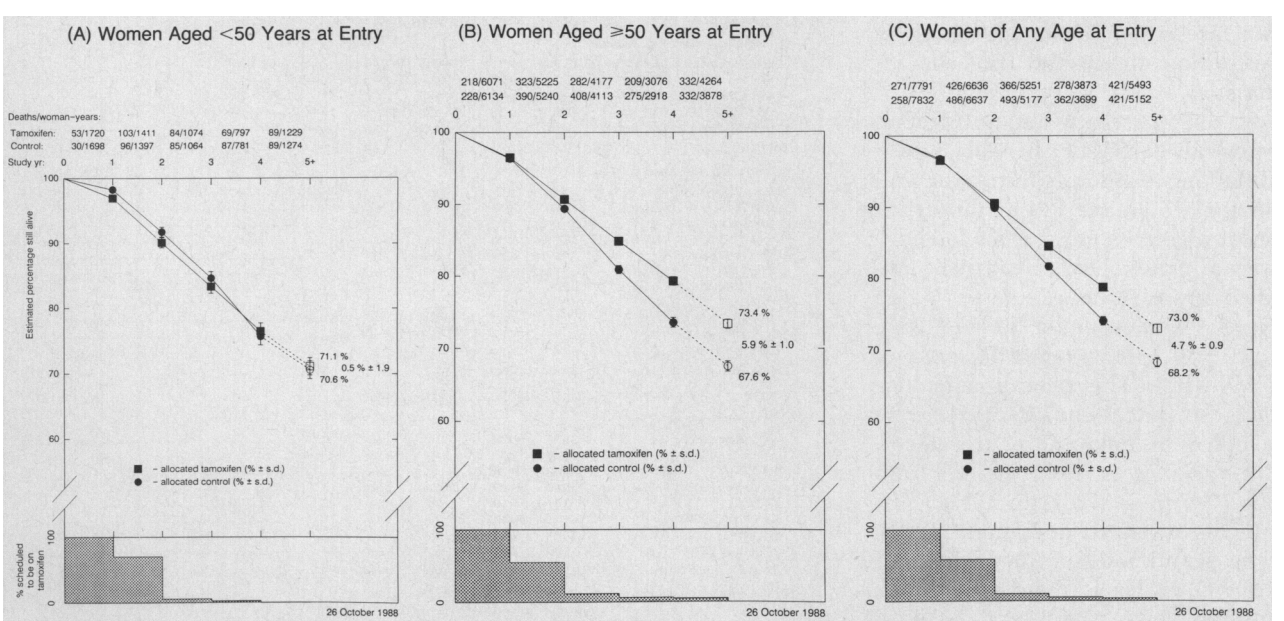


Figure 2. Estimated Survival among Women in All Available Trials Comparing Tamoxifen with No Tamoxifen Regimen (Including Trials with an Identical Tamoxifen Regimen in Both Treatment and Control Groups).

Open squares or circles, along with dashed lines, are used for year 5+ since the last period is open-ended.

is apparent, but among older women (Fig. 2B), the 5.7 percent absolute difference in five-year survival had a high level of significance ($P<0.00001$). In most trials, treatment was stopped after one or two years, but during the subsequent years prior tamoxifen therapy delayed or prevented substantial numbers of deaths among older women. The apparent difference between the sizes of the effect during the first two years and the effect during the subsequent years was not statistically significant (and remained nonsignificant when only trials with follow-up beyond year 2 were analyzed).

Indirect Comparisons: Dose, Duration of Treatment, and Addition of Chemotherapy

Table 2 shows reductions in mortality according to the dose of tamoxifen tested (20 mg per day or 30 to 40 mg per day), the duration of tamoxifen administration (two years or longer, or one year or less), and the concomitant use of chemotherapy (tamoxifen vs. no adjuvant therapy, or tamoxifen plus chemotherapy vs. the same chemotherapy alone). Although more prolonged use of tamoxifen appeared to be somewhat more effective, this "interaction" was not statistically significant, nor were the other two interactions shown in Table 2.

Chemotherapy Trials

The results of 31 trials comparing adjuvant chemotherapy with no chemotherapy, along with an overview of the effect of chemotherapy in all the trials together, are presented in Figure 3, again according to age and trial characteristics.

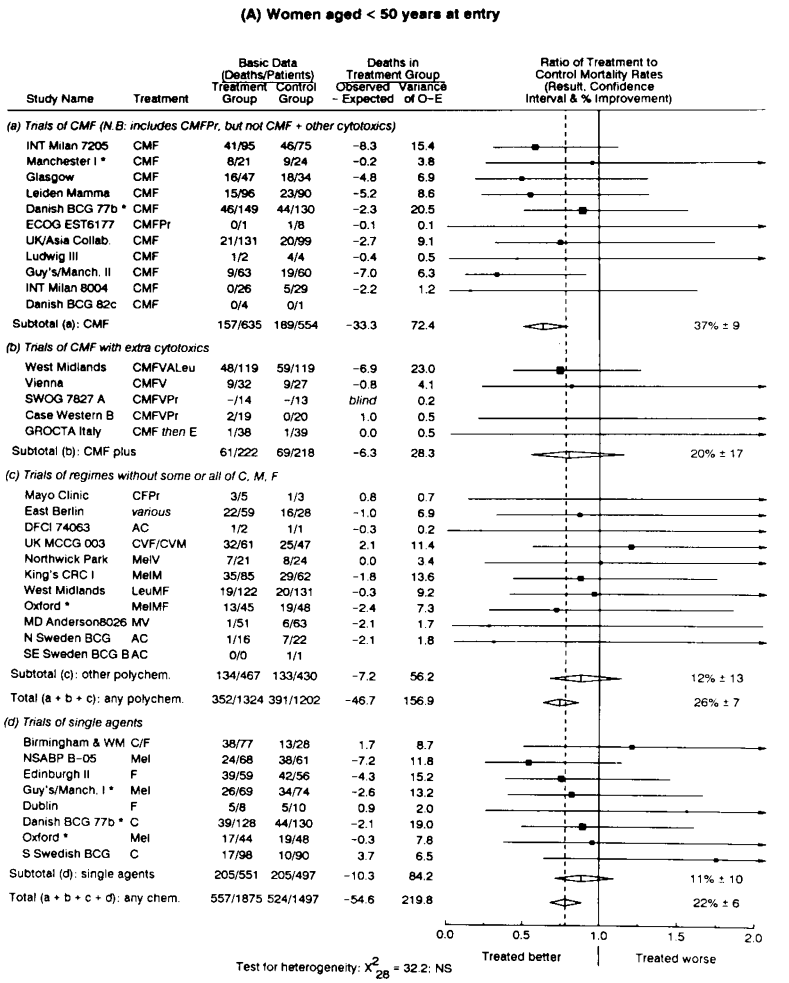
If chemotherapy had no effect on survival, each O − E value would differ only randomly from zero, and so too would the grand total. But most of the O − E values for individual trials were negative, and their grand total is −71.7 (−54.6 for the women under 50 [Fig. 3A], and −17.1 for women 50 or over [Fig. 3B]). This overall difference suggests that about 140 deaths were avoided or delayed by treatment. Its variance is 592.9 (219.8 from Fig. 3A plus 373.1 from Fig. 3B) and its standard deviation is 24.3. The grand total of the individual O − E values is therefore 2.9 SD below zero (i.e., $z = -2.9 = -71.7/24.3$; $P = 0.003$). The reduction in the odds of death among women of all ages who were as-

Table 2. Indirect Comparisons of the Effects of Different Tamoxifen Regimens on Mortality.

	Typical Reduction in Annual Odds of Death (% ±SD)			
	Age <50	Age ≥50	Any age*	
Dose of tamoxifen				
20 mg/day vs. no tamoxifen	−5±9	22±5	17±4	NS
30–40 mg/day vs. no tamoxifen	8±14	18±5	16±5	
Duration of tamoxifen treatment				
≤1 yr vs. no tamoxifen	−7±15	15±6	11±6	NS
≥2 yr vs. no tamoxifen	+1±9	23±4	19±4	
Interaction of tamoxifen with chemotherapy				
Tamoxifen vs. no adjuvant therapy	21±14	19±4	19±4	NS
Tamoxifen + chemotherapy vs. same chemotherapy	−9±9	22±6	16±5	
Any tamoxifen vs. no tamoxifen (95% confidence interval)	−1±8 (−17 to 13)	20±3 (14 to 26)	16±3 (10 to 22)	

*Standardized for age (under or over 50) as follows: Since one fifth of all information relates to women under 50, the age-standardized mortality reduction was defined as 0.2 × mortality reduction among younger women plus 0.8 × mortality reduction among older women.

NS denotes not significant.



* control patients in 3-way trials (polychem. vs. single agent vs. no cytotoxic) contribute to 2 subtotals but only once to the grand total and χ^2.

signed to chemotherapy was 14(±4) percent. Chance alone cannot plausibly account for this observed difference, which therefore provides clear evidence that for some types of women, adjuvant chemotherapy can prolong survival.

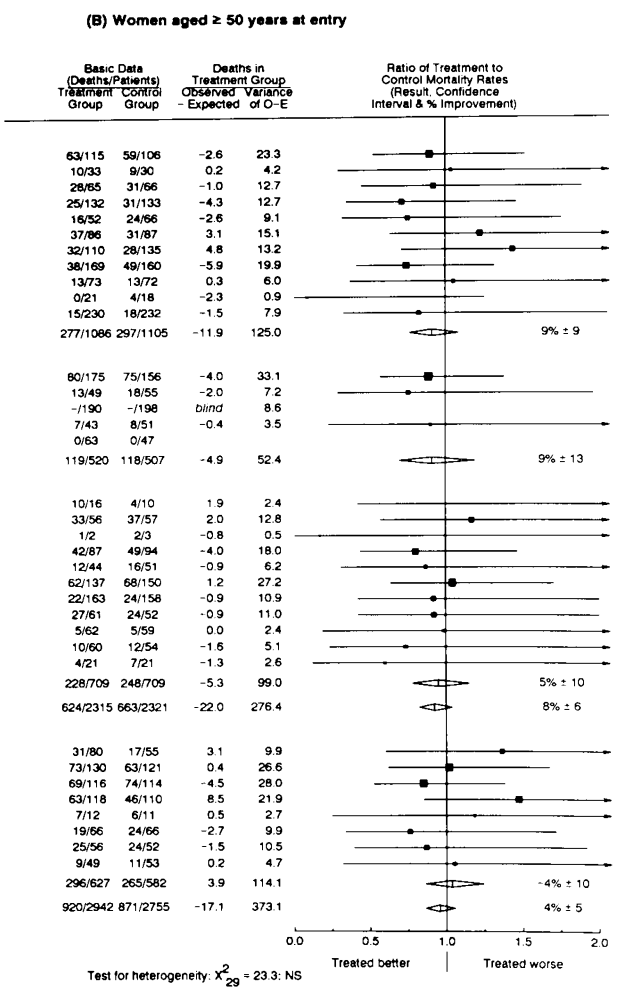
Heterogeneity of Effects

A chi-square test of heterogeneity between the results of the 31 trials listed in Figure 3 gave a nonsignificant result (29.6 with 30 degrees of freedom). But, as noted above, such tests lack power. Moreover, different categories of patients may respond quite differently and different regimens may not be equally effective. Therefore, the data from individual chemotherapy trials have been grouped according to specific patient variables (e.g., age) and treatment regimens (e.g., the number of drugs employed or the type of polychemotherapy regimen).

Indirect Comparisons: Age

In contrast with tamoxifen, which had its clearest effect among the older women, the chemotherapy regimens employed in these trials had their clearest effect among the younger women. Among those under 50, the reduction in the annual odds of death was 22(±6) percent (P = 0.0002). Among women 50 or older, there was no clear evidence from these analyses that chemotherapy reduces mortality. The estimated difference between the effects of chemotherapy in these two age groups was statistically significant (P = 0.02), but the 95 percent confidence interval for the effect of chemotherapy on mortality among women 50 or older was wide, ranging from a 6 percent adverse effect to a 14 percent benefit.

The graphic display of the odds ratio determined for each study (Fig. 3) illustrates the variability in the apparent size of the effect of chemotherapy and even in the apparent direction of the effect (beneficial or detrimental). Although the 99 percent confidence interval overlay unity in both age groups for almost all the trials, the overview estimates and the 95 percent confidence interval were to the left of unity (demonstrating significant benefit) for women under 50. However, the 95 percent confidence interval for the overview estimate overlay unity for the older women.



Indirect Comparisons: Different Drug Regimens

The results of randomized trials comparing single-agent chemotherapy with no chemotherapy and those comparing combination chemotherapy regimens with no chemotherapy are shown in Table 3. Indirect comparison of these overall results suggested that polychemotherapy may be more effective than single-agent chemotherapy, and direct comparisons from randomized trials, which provide a better basis for inference, reinforced this (see below). The mortality results are also grouped according to the concomitant use of tamoxifen (chemotherapy vs. no chemotherapy, and chemotherapy plus tamoxifen vs. the same tamoxifen regimen). The effects of chemotherapy in the presence or absence of tamoxifen were not significantly different from each other.

The chemotherapy regimens that have been most extensively studied in these trials consisted of cyclophosphamide–methotrexate–fluorouracil (CMF) or CMF plus other cytotoxic agents. Reductions in mor-

Figure 3. Mortality among Women in All Available Trials Comparing Prolonged Cytotoxic Therapy with Control Treatment without Cytotoxic Agents (Including Trials with an Identical Tamoxifen Regimen in Both Treatment and Control Groups).

The grand totals are not equal to the sums of the results for the separate trials because a few trials involved three-way treatment assignment between polychemotherapy, single-agent chemotherapy, and control. If the results for the comparison of polychemotherapy with control treatment and the results for comparison of single-agent chemotherapy with control treatment are just added, then the control group would be counted twice, whereas it should be counted only once in comparisons of any chemotherapy with control.

For an explanation of the symbols and conventions, see legend to Figure 1.

Table 3. Direct and Indirect Comparisons of the Effects of Different Chemotherapy Regimens on Mortality.

	Typical Reduction in Annual Odds of Death (% ±SD)		
	Age <50	Age ≥50	Any age*
Comparisons of single agent and polychemotherapy			
Single-agent chemotherapy vs. no chemotherapy	11±10	−4±10	4±7
Polychemotherapy vs. no chemotherapy	26±7	8±6	17±5
Polychemotherapy vs. single-agent chemotherapy	21±9	17±8	19±6
Interaction of chemotherapy with tamoxifen			
Chemotherapy vs. no adjuvant therapy	22±6	3±5	12±4
Chemotherapy + tamoxifen vs. same tamoxifen regimen	31±30	12±13	22±16
Any chemotherapy vs. no chemotherapy (95% confidence interval)	22±6 (11 to 32)	4±5 (−6 to 14)	14±4 (6 to 22)
Prolonged vs. less prolonged chemotherapy	−8±12	−12±12	−10±8

*Standardized for age (under or over 50) as a simple average of the reduction for older and for younger women.

tality with these chemotherapy regimens are shown as subtotals in Figure 3. A comparison of these subtotals suggests that regimens including CMF may be somewhat more effective than some of the other polychemotherapy regimens, but the advantage of CMF-based regimens over other regimens is not statistically significant. The number of patients in trials not including CMF is small, and the regimens vary considerably in their intensity of treatment, the number of drugs employed, and the effectiveness of the individual drugs.

Direct Comparisons: Number of Drugs and Duration of Therapy

In contrast with the assessment of tamoxifen (for which there are as yet few direct randomized comparisons of different treatment durations), second-generation chemotherapy trials have involved direct comparisons of combination regimens with single agents as well as direct comparisons of regimens of different durations. The results of the direct comparisons of polychemotherapy with single-agent chemotherapy were significantly in favor of polychemotherapy (Fig. 4), especially when the results in women of all ages are combined. These findings are also summarized in Table 3.

Several direct randomized comparisons have been made between more prolonged regimens (e.g., 6 to 24 months) and less prolonged regimens (e.g., 3 to 6 months). Review of these direct comparisons (Fig. 5) did not indicate that prolonged treatment had any survival advantage over less prolonged treatment. If anything, it suggested the opposite, since combining the results in older and younger women (Fig. 5) indicates a nonsignificant difference of 10(±8) percent in favor of less prolonged therapy (Table 3).

Effects of Treatment According to Year of Follow-up

The survival curves shown in Figure 6 describe the estimated effects of polychemotherapy compared with no chemotherapy in each year of follow-up. There is a moderate but highly significant effect among women under 50 years of age, but no clearly significant effect on mortality among older women. Among the younger women there is no evidence that these early gains were lost within the first five years. Since the tails of survival curves can be quite unstable, longer follow-up is needed to verify this conclusion (and, of course, to study longer-term survival).

Nodal Status and Estrogen-Receptor Status

Among women undergoing lymph-node dissection, there was evidence of lymph-node involvement in 6739 of 11,824 women (57 percent) in trials comparing tamoxifen with no tamoxifen, and 4344 of 5933 (73 percent) in trials comparing chemotherapy with no chemotherapy. The main report[1] on the collaboration presented in this overview contains separate analyses of outcome among patients with a poor prognosis (e.g., those with metastatic involvement of at least four axillary lymph nodes) and among patients with

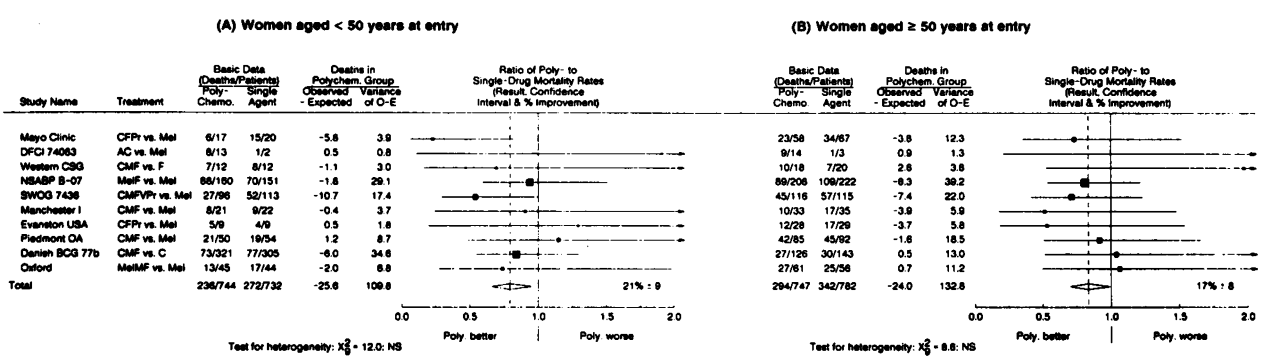


Figure 4. Mortality among Women in All Available Trials Comparing Prolonged Multiple-Agent Cytotoxic Therapy with Single-Agent Cytotoxic Therapy (Including Trials with an Identical Tamoxifen Regimen in Both Treatment and Control Groups).
For an explanation of the symbols and conventions, see legend to Figure 1.

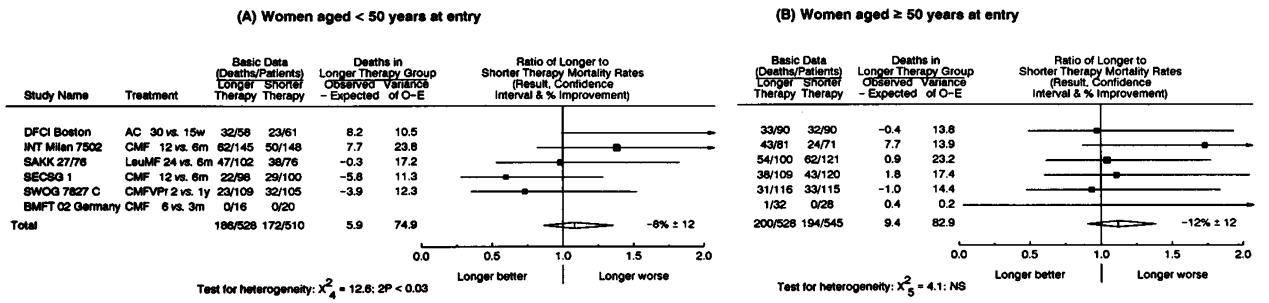


Figure 5. Mortality among Women in All Available Trials Comparing Prolonged Cytotoxic Therapy with Less Prolonged Cytotoxic Therapy (Including Trials with an Identical Tamoxifen Regimen in Both Treatment and Control Groups).
For an explanation of the symbols and conventions, see legend to Figure 1.

less extensive disease (e.g., those with no or only one to three nodes involved). With tamoxifen and with polychemotherapy, the proportional reductions in the annual death rates during the first five years were not clearly different in these different categories of women. However, only a limited amount of information was available on women without nodal involvement. So, although the proportional reductions in mortality among women with and without nodal involvement appeared to be similar, for neither form of adjuvant treatment is the mortality reduction statistically significant in an analysis restricted to patients with negative nodes.

Measurements of estrogen-receptor (ER) levels were available for nearly half the patients in the tamoxifen trials. Patients were classified as "estrogen-receptor–poor" if the level was less than 10 fmol per milligram of protein or if the tumor was described by the principal investigator as "ER−." Patients with levels of 10 fmol or more and patients described as "ER+" or "ER++" were classified as "estrogen-receptor–rich." The prognosis of women classified as estrogen-receptor–poor was substantially worse than that of women classified as estrogen-receptor–rich, suggesting that this estrogen-receptor classification had some biologic meaning. However, it did not identify a group of patients wholly unresponsive to tamoxifen. The limitations of these assay techniques and of inferences based on them are discussed, along with additional data, in the main report of this collaboration.[1]

Discussion

This overview of adjuvant trials has established beyond reasonable doubt that both tamoxifen and cytotoxic chemotherapy can reduce five-year mortality. Furthermore, since not all patients complied with the treatment assigned, the trials tended to underestimate the size of the treatment benefits among patients who did comply. Even with the size of the present over-

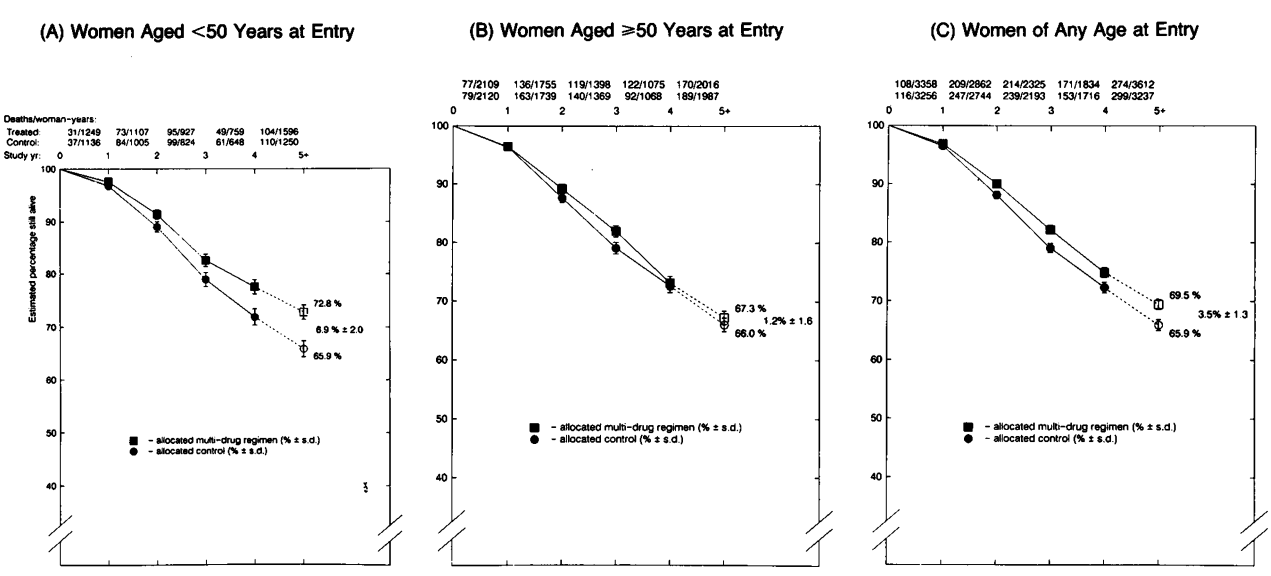


Figure 6. Estimated Survival among Women in All Available Trials Comparing Polychemotherapy with Control Treatment without Cytotoxic Agents (Including Trials with an Identical Tamoxifen Regimen in Both Treatment and Control Groups).
For an explanation of the symbols and conventions, see legend to Figure 2.

view, however, it is difficult to identify reliably the treatments that are most effective or the subgroups of patients who are most likely to benefit, since separate analyses of mortality in subgroups of the total populations are liable to be unduly influenced by the play of chance.

The mortality reduction produced by tamoxifen was most certain among women 50 or older (20[±3] percent; with the most extensively tested tamoxifen regimens involving doses of at least 20 mg per day for at least two years). In contrast, the effects of polychemotherapy were most certain among women under the age of 50 (26[±7] percent; with the most extensively tested regimens based on CMF). Direct randomized comparisons did not provide any evidence that prolonged chemotherapy was more effective than somewhat less prolonged treatment. However, it is not possible to define a single optimal duration of chemotherapy, since this may vary with the chemotherapeutic agents used. There is no reason to suppose that either the tamoxifen or the chemotherapy regimens tested represent the best that these treatments can offer.

An appreciable effect of tamoxifen on mortality among younger women has not been demonstrated by the trials, but neither can it be ruled out by the available data, partly because of sample-size limitations and partly because among younger women tamoxifen was generally studied only in combination with chemotherapy. Tamoxifen alone, in the absence of chemotherapy, was tested in 9061 older women but in only 1062 younger women. Although tamoxifen appeared to be equally effective among older women when administered alone or in combination with chemotherapy, there is still the possibility of a negative interaction between these two modalities, particularly in younger women.

Clear survival benefits from chemotherapy were not evident in women of 50 or more. The number of older women entered into trials comparing chemotherapy with no chemotherapy was larger than the number under 50. Despite this, the slight trend toward improved survival in women 50 or older failed to reach statistical significance, and the advantage of polychemotherapy over single-agent chemotherapy among older women had an only marginal level of significance. Chemotherapy did, however, significantly reduce recurrence rates among both younger and older women[1] — as, indeed, did tamoxifen — which suggests that any differences between the effect of treatment on mortality among younger and older women are likely to be in the sizes of the effects (i.e., "quantitative") rather than in their direction (i.e., "qualitative").[6]

Some indirect comparisons between the sizes of the treatment effects are inevitable, especially when variables cannot be subjected to randomization (e.g., age) or when data from randomized comparisons are limited. In this overview, indirect comparisons have been made of the duration of tamoxifen treatment, the optimal dose of tamoxifen, and the effects of CMF and those of other combination chemotherapy regimens. Such indirect comparisons may serve to generate hypotheses to be tested in future trials, but they need to be interpreted extremely cautiously. For, although many of the biases inherent in nonrandom methods (such as those involving historical controls) are avoided by comparing differences between treatments observed in randomized trials in one circumstance with differences observed in randomized trials in another circumstance, some potential for bias remains.[1] Comparisons of the apparent effects of tamoxifen with those of chemotherapy are not, however, appropriate, since the effects of these different treatment regimens may be largely independent.

Additional years of follow-up may appreciably alter the interpretation of the results of this overview, especially as they apply to particular subgroups. For example, if proportional reductions in mortality are initially similar among patients with a poor prognosis and among those with a good prognosis, then — at least during the first few years of follow-up — the absolute mortality reductions produced by treatment will be greatest in those with a poor prognosis. However, with further follow-up this may not continue to be the case, and if any clear differences in mortality are still apparent after 10 or 15 years, the greatest absolute differences might then be among women who initially had a reasonably good prognosis. The interpretation of the long-term effects of treatment may also be helped by analyses of cause-specific mortality occurring before disease recurrence, both to check against any adverse effects of treatment and to help avoid dilution of any favorable effects of treatment by deaths due to unrelated causes. Much more information is still required from randomized trials in various groups of patients about the effects of these and related treatments (e.g., more prolonged hormonal therapy or more intensive chemotherapy).

Implications for Treatment

Treatment depends on a wide range of considerations, of which trial results are only one part. Hence, the present report makes no recommendations about what treatments should be prescribed (nor does it deal with practical aspects of the dosages or side effects of any of the treatments considered, which have been reviewed by others[7]). Trial results (or overviews of them) provide information, not instructions. When individual trials or overviews do provide definite answers, physicians who treat early breast cancer have a responsibility merely to become aware of those answers (and of any important limitations in the methods that produced them), in order that they may bear them in mind when recommending treatments. Physicians should thus be aware of the approximate size and of the great statistical stability of the reductions in five-year mortality observed in trials of

polychemotherapy in younger women and of tamoxifen in older women. The relevance of these reductions to long-term survival is uncertain, however, and will be addressed in future overviews of these and other trials.

The scientific stimuli for this collaboration were the Clinical Trial Service Unit of the Imperial Cancer Research Fund and the Medical Research Council, the Breast Trials Unit of the Cancer Research Campaign, the U.K. Breast Cancer Trials Co-ordinating Subcommittee, the Project on Controlled Therapeutic Trials of the Union Internationale Contre le Cancer, and the Cancer Office of the World Health Organization.

We are indebted to the thousands of women who took part in the trials, and to the many medical, statistical, and administrative trial investigators who carefully checked any queries and provided detailed information on the trials.

Appendix

The trials included in these overviews are listed below, with a short name (as used in Fig. 1 and 3 through 5), the year (in parentheses) in which the trial was begun, the name or location of the institution or study group, and the regimens compared.

An asterisk denotes that data were available only for certain periods, disease stages, or age groups. The following abbreviations are used in the listing of the regimens. A denotes doxorubicin (Adriamycin), BCG Bacillus Calmette–Guérin, C cyclophosphamide, DES diethylstilbestrol, E 4′-epidoxorubicin, F fluorouracil, Leu chlorambucil (Leukeran), Lev levamisole, M methotrexate, Mel melphalan (L-phenylalanine mustard), Nil none of the systemic therapies employed in other treatment areas, OvXRt irradiation of ovaries, Pr prednisone, T tamoxifen, V vincristine/vinblastine, and XRt radiotherapy.

Birmingham (67): Birmingham and West Midlands Cancer Registry, U.K. 1, C ×12 mo; 2, F ×12 mo; 3, nil.

BMFT 02 Germany (84): Multicentre Group. 1, CMF ×3 mo; 2, same + T ×24 mo; 3, CMF ×6 mo; 4, same + T ×24 mo.

Case Western A (74): Case Western Reserve University, U.S. 1, CMF ×12 mo; 2, CMFT ×12 mo; 3, CMFT + BCG ×12 mo.

Case Western B (79). T ×36 mo + (1, OvXRt; 2, CMFVPr ×12 mo; 3, both; 4, nil).

Christie B (76): Christie Hospital, U.K. 1, T ×12 mo; 2, nil.

Copenhagen (75): Copenhagen Breast Cancer Trials, Denmark. 1, T ×24 mo; 2, * DES ×24 mo; 3, nil.

CRC 2 (80): Cancer Research Campaign, U.K. 1, T ×24 mo; 2, C ×6 days; 3, both; 4, nil.

CRFB Caen C5 (78): Centre Regional François Baclesse. 1, T ×36 mo; 2, nil.

Danish BCG 77b (77): Danish Breast Cancer Group. 1, C ×12 mo; 2, CMF ×12 mo; 3, * Lev; 4, * nil.

Danish BCG 77c (77): 1, T ×12 mo; 2, * Lev; 3, nil.

Danish BCG 82b (82): 1, CMF ×9 mo; 2, same + XRt; 3, CMF ×9 mo + T ×12 mo.

Danish BCG 82c (82): 1, XRt + T ×12 mo; 2, T ×12 mo; 3, CMF ×9 mo + T ×12 mo.

DFCI 74063 (74): Dana–Farber Cancer Institute, U.S. 1, AC ×3.5 mo; 2, AC ×7 mo; 3, * nil; 4, * Mel ×24 mo.

Dublin (76): Dublin, Eire. 1, F ×12 mo; 2, nil.

East Berlin (74): Akademie der Wissenschaften der DDR. 1, varied chemotherapy ×24 mo; 2, nil.

ECOG EST 1178 (78): Eastern Cooperative Oncology Group, U.S. 1, T ×24 mo; 2, nil.

ECOG EST 5177 (77). 1, CMF ×12 mo; 2, CMFPr ×12 mo; 3, CMFPrT ×12 mo.

ECOG EST 6177 (77). 1, CMFPr ×12 mo; 2, CMFPrT ×12 mo; 3, nil.

Edinburgh II (74): Scottish Cancer Trials Office, U.K. 1, F ×12 mo; 2, nil.

Evanston USA (75): Evanston and Chicago hospitals, U.S. 1, Mel ×12 mo; 2, CFPr ×12 mo; 3, CFPr + BCG ×12 mo.

FB Bordeaux (81): Fondation Bergonie B, France. 1, CMF ×27 wk; 2, same + T ×24 mo.

GABG W. Germany (79): Gynecologic Adjuvant Breast Group, F.R.G. 1, AC ×6 mo; 2, T ×24 mo; 3, both; 4, nil.

Ghent University (79): Belgian Multicentre Trial. 1, T ×24 mo; 2, nil.

Glasgow (76): Glasgow, U.K. 1, CMF ×12 mo; 2, XRt; 3, both.

GROCTA Italy (83): Chemohormonal Therapy Group, Italy. 1, T ×60 mo; 2, CMF ×6 mo, then E ×4 mo; 3, both.

GUN Naples (78): University of Naples, Italy. 1, T ×24 mo; 2, CMF ×9 mo; 3, both; 4, nil.

Guys CMF (79): Guy's Hospital, U.K. 1, CMF ×12 mo; 2, nil.

Guys L-Pam (75). 1, Mel ×24 mo; 2, nil.

Innsbruck (78): Austrian Multicentre Trial. 1, T ×12 mo; 2, nil.

INT Milan 7205 (73): Istituto Nazionale dei Tumori, Italy. 1, CMF ×12 mo; 2, nil.

INT Milan 7502 (75). 1, CMF ×6 mo; 2, CMF ×12 mo.

INT Milan 8004 (80). 1, CMF ×12 mo; 2, nil.

Kings CRC I (75): King's College Hospital, U.K. 1, MelM ×24 mo; 2, nil.

Leiden Mamma (76): EORTC Dutch Breast Working Party. 1, CMF ×24 mo; 2, nil.

Ludwig III/IV (78): Ludwig Breast Cancer Study Group. 1, PrT ×12 mo; 2, * CMFPrT ×12 mo; 3, nil.

Manchester I (75): University Hospital, South Manchester, U.K. 1, Mel ×24 mo; 2, CMF ×12 mo; 3, nil.

Manchester II (79). 1, CMF ×12 mo; 2, nil.

Mayo Clinic (73): Mayo Clinic, U.S. 1, CFPr ×12 mo; 2, *XRt; 3, both; 4, *nil; 5, * Mel ×12 mo.

MD Anderson 8026 (80): M.D. Anderson Hospital, U.S. 1, FACVPr ×7.5 mo, then T ×6 mo; 2, same + MV ×6 mo.

Montpellier (81): Montpellier, France. 1, T ×24 mo; 2, nil.

N. Sweden BCG 192 (80): North Sweden Breast Cancer Group. 1, T ×24 mo; 2, nil.

N. Sweden BCG 193 (80). 1, OvXRt + T ×24 mo; 2, AC ×8 mo; 3, both; 4, nil.

N. Sweden BCG 194 (80). 1, T ×24 mo; 2, AC ×8 mo; 3, both; 4, nil.

NATO (77): Nolvadex Adjuvant Trial Organization, U.K. 1, T ×24 mo; 2, nil.

Northwick Park (75): Northwick Park Hospital, U.K. 1, MelV ×12 mo; 2, nil.

NSABP B05 (73): National Surgical Adjuvant Breast Project, U.S. 1, Mel ×24 mo; 2, nil.

NSABP B07 (74). 1, Mel ×24 mo; 2, MelF ×24 mo.

NSABP B09 (76). 1, MelF ×24 mo; 2, MelFT ×24 mo.

Oxford (77): Oxford, U.K. 1, Mel ×24 mo; 2, MelMF ×24 mo; 3, nil.

Piedmont OA (75): Piedmont Oncology Assoc, U.S. 1, Mel ×24 mo; 2, same + XRt; 3, CMF ×24 mo; 4, same + XRt.

S. Swedish BCG (78): South Swedish Breast Cancer Group. 1, XRt; 2, C ×12 mo; 3, both; 4, XRt + T ×12 mo.; 5, T ×12 mo.

SAKK 27/76 (75): Swiss Group for Clinical Research. 1, LeuMF ×6 mo; 2, LeuMF ×24 mo.

Scottish (78): Scottish Cancer Trials Office. 1, T ×≥60 mo; 2, nil.

S.E. Sweden BCG B (80): Southeast Sweden Breast Cancer Group. 1, AC ×6 mo; 2, nil.

SECSG 1 (76): Southeastern Cancer Study Group, U.S. 1, * CMF ×12 mo; 2, CMF ×6 mo; 3, * same + XRt.

Stockholm B (76): Stockholm Breast Cancer Study Group, Sweden. 1, * T×24 mo; 2, * CMF ×12 mo; 3, * both; 4, * XRt; 5, * XRt + T×24 mo; 6, * nil.

SWOG 7436 (75): Southwest Oncology Group, U.S. 1, Mel ×24 mo; 2, CMFVPr ×12 mo.

SWOG 7827A (79). 1, T ×12 mo; 2, CMFVPr ×12 mo; 3, both.

SWOG 7827C (79). 1, CMFVPr ×12 mo; 2, CMFVPr ×24 mo.

Toronto-Edmont. (78): Toronto–Edmonton Breast Cancer Study Group, Canada. 1, T ×24 mo; 2, nil.

Toulouse (80): Centre Claudius Regaud, France. 1, T ×24 mo; 2, nil.

U.K. MCCG 003 (74): Multicentre Breast Cancer Goup, U.K. 1, CMFV ×6 mo; 2, nil.

U.K. MCCG 009 (77). 1, LeuMFV ×6 mo; 2, * same, then T ×6 mo; 3, CMFV ×6 mo; 4, * same, then T ×6 mo; 5, T ×12 mo.
U.K./Asia Collab (78). 1, CMF ×24 mo; 2, T ×24 mo; 3, both; 4, nil.
Vienna (77): University of Vienna, Austria. 1, CMFV ×36 mo; 2, same + azimexon; 3, nil.
West Midlands A (76): West Midlands Oncology Association, U.K. 1, AVLeuCMF ×6 mo; 2, LeuMF ×6 mo; 3, nil.
Western CSG (74): Western Cancer Study Group, U.S. 1, F ×12 mo; 2, CMF ×12 mo.

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ACYCLOVIR TREATMENT OF THE CHRONIC FATIGUE SYNDROME

Lack of Efficacy in a Placebo-Controlled Trial

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Abstract Twenty-seven adults with a diagnosis of the chronic fatigue syndrome were enrolled in a double-blind, placebo-controlled study of acyclovir therapy. The patients had had debilitating fatigue for an average of 6.8 years, accompanied by persisting antibodies to Epstein–Barr virus early antigens (titers ≥1:40) or undetectable levels of antibodies to Epstein–Barr virus nuclear antigens (titers <1:2) or both. Each course of treatment consisted of intravenous placebo or acyclovir (500 mg per square meter of body-surface area) administered every eight hours for seven days. The same drug was then given orally for 30 days (acyclovir, 800 mg four times daily). There were six-week observation periods before, between, and after the treatments.

Three patients had acyclovir-induced nephrotoxicity and were withdrawn from the study. Of the 24 patients who completed the trial, similar numbers improved with acyclovir therapy and with placebo (11 and 10, respectively). Neither acyclovir treatment nor clinical improvement correlated with alterations in laboratory findings, including titers of antibody to Epstein–Barr virus or levels of circulating immune complexes or of leukocyte 2′,5′-oligoadenylate synthetase. Subjective improvement correlated with various measures of mood.

We conclude that acyclovir, as used in this study, does not ameliorate the chronic fatigue syndrome. We believe that the clinical improvement observed in most patients reflected either spontaneous remission of the syndrome or a placebo effect. (N Engl J Med 1988; 319: 1692-8.)

A SYNDROME characterized by debilitating fatigue, diffuse pains, sore throat, tender lymph nodes, mild fever or feelings of feverishness, decreased ability to concentrate, and depression has become the subject of considerable interest and speculation in both the medical and lay communities.[1] Although similar illnesses have been described for many decades, a series of papers published between 1982 and 1985 rekindled broad interest in this syndrome.[2-5] They reported that subtle immunologic abnormalities and unusual profiles of antibodies to Epstein–Barr virus antigens are unexpectedly common in the syndrome. Specifically, the levels of antibodies to viral capsid antigens of Epstein–Barr virus and to early antigens of the diffuse or restricted type were higher in patients than in controls. In addition, a subset of patients was found to lack antibodies to one or all Epstein–Barr virus nuclear antigens (EBNAs). Because these serologic patterns emerge during active Epstein–Barr virus infections and because the syndrome is occasionally precipitated by infectious mononucleosis, it was proposed that the syndrome represents chronic Epstein–Barr virus infection. More thorough appraisals of viral seroepidemiology, however, argued against a major etiologic role of Epstein–Barr virus in the syndrome.[6,7] A working group at the Centers for Disease Control recently renamed this disorder the chronic fatigue syndrome.[8]

The plight of patients with the syndrome has encouraged a variety of compassionate approaches to treatment. Among these has been the use of acyclovir,

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