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COMMENTARY

The Methodologic Dilemma in Retrospectively Correlating the Amount of Chemotherapy Received in Adjuvant Therapy Protocols With Disease-Free Survival^{1,2}

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When carrying out a study to evaluate the worth of a chemotherapeutic regimen it is important that the amount of drug received by the patients is consistent with that prescribed by the protocol. For various reasons a substantial number of patients may not have received the quantity planned. As a consequence, the study may be rejected, since conclusions cannot be formulated regarding the value of the treatment. On the other hand, the results may be accepted as found and considered representative of what would be expected if the regimen were to be employed on a population as a whole. Alternatively, an attempt may be made to obtain, retrospectively, information which could be used to relate the amount of drug received by patients to their outcome even though that correlation was not one of the original aims of the investigation.

Recently, a retrospective analysis was made of patients who had been entered into a prospective randomized trial to evaluate the worth of cyclophosphamide, methotrexate, and 5-FU (CMF) as adjuvant therapy for breast cancer. A report of that analysis indicated that the disease-free survival of patients was directly related to the amount of drug received (1). Other investigators also considered their findings according to the proportion of the protocol dose which was received (2-4). We have attempted to correlate the amount of drug received with disease-free survival by retrospectively examining information from two National Surgical Adjuvant Breast and Bowel Project (NSABP) trials in which adjuvant therapy was administered for 2 years (5,6). That undertaking has emphasized the methodologic difficulties encountered when making such an analysis and the hazard of drawing conclusions from the findings.

THE PROBLEM

A number of serious methodologic problems arise that make this type of post hoc analysis difficult to perform. When contemplating such a retrospective evaluation, and prior to analyzing the information obtained, it is imperative that several major issues be resolved. The first is to decide upon the appropriate manner in which to summarize the amount of drug that the patient has received. Should one accumulate the total amount given in all of the courses and use that value, or should one convert it into a percentage of the maximum contemplated protocol dose and employ that measure in the correlation with patient outcome? What should be done when several different drugs are given in combination? Should the doses of each of the drugs be combined into a single dose to arrive at an overall measure of "dose" given, or should a weighted average of each of the drugs be employed? When a decision is reached on how best to determine the amount of drug that the patient has received, it must then be decided how best to correlate that amount with treatment failure and survival of patients. Should they be stratified according to dose levels, and how might those levels be selected? Should the results be examined from the time therapy was initiated, or should they be evaluated only subsequent to completion of therapy? Are there statistical approaches which enable one to take into account the cumulative nature of the amount of drug received?

POTENTIAL METHODS FOR RESOLVING THE PROBLEM

Several definitions of the dose of drug(s) that a patient has received may be considered.

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Method I

The first method calculates the amount of drug taken by each patient, without consideration of any of the factors which may have led to a reduction or cessation of the therapy:

$$\text{amount of drug received (\%)} = \frac{\text{total of all drug received}}{\text{maximum protocol dose (full protocol dose at each course} \times \text{protocol No. of courses})} \times 100.$$

The following indicates how the use of this most obvious approach for determining amount of drug received produces biased results. Using data from NSABP protocols, the amount of melphalan [L-PAM (P)] or P + 5-FU (PF) received was calculated. Patients, whether receiving P or PF, were grouped into three levels according to whether they received $\geq 85\%$ (Level I), 65%-84% (Level II), or $< 65\%$ (Level III) of the protocol-stipulated dose of P. The level of P and of F was found to be similar in PF-treated patients, eliminating the need for averaging the proportion of the two drugs received. Life tables were then constructed for each of the groups. The distribution of patients at each dose level and the life-table disease-free survival at 5 years for those receiving P (table 1) and at 4 years for those receiving PF (table 2) are shown. When P was given, there was little difference in the proportion of the patients ≤ 49 or ≥ 50 years old (about 35%) who received the maximum (Level I) amount of drug. With PF, more of the patients ≥ 50 than ≤ 49 years old received the Level I amount. Only 6% of the older patients got $< 65\%$ of the protocol dose, while 30% of the younger women were in the Level III group, indicating that the older women tolerated the drug as well as, if not better than, did the younger age group.

The data demonstrate a consistent difference in disease-free survival among P- or PF-treated patients at the three dose levels. This was observed whether they were considered overall or according to age and nodal status. Increasing dose was associated with increasing disease-free survival. In some instances Level III was associated with a poorer disease-free survival than that observed in the control group. At times, the difference was quite marked. This observation is exemplified by patients ≥ 50 years of age with 1-3 positive nodes. Those receiving $< 65\%$ of P had a disease-free survival which was 24% lower than that for the untreated control patients. Since the overall results in that subgroup, without regard for dose received, indicate no difference between treated and nontreated patients, the disparity observed in patients receiving the Level III amount of drug must of necessity be associated with a compensatory benefit in those getting the Level I amount. In this example, acceptance that more drug is associated with a benefit requires that there be a similar acceptance that the least amount of drug is harmful. Consequently, the presence of a significant dose/response relationship in an otherwise negative comparison of drug-treated patients to controls, as in this group of patients, poses difficulties in interpretation.

The greater disease-free survival in Level I patients is due to the fact that those who failed early were automatically excluded from this group because protocol treatment is stopped at failure; they were not receiving therapy long enough to have accumulated $\geq 85\%$ of the protocol amount, even if they had received full doses up to the time of recurrence. The patients with early failures, therefore, concentrate in the low-dose groups and thus account for the decreased probability of disease-free survival in those given the Level III amount of drug. The bias produced by this method of determining drug dose

TABLE 1.—% disease-free survival at 5 yrs, by % dose level for P (Method I)

Age and nodal status	Dose level *			Any dose *	Control *	P value†
	I ($\geq 85\%$)	II (65%-84%)	III (< 65%)			
All patients	69 (182)	67 (140)	26 (201)	51 (525)	46 (505)	$< 10^{-5}$
≤ 49 yrs	71 (77)	80 (46)	20 (79)	52 (203)	37 (170)	$< 10^{-5}$
1-3 positive	73 (53)	92 (25)	29 (29)	66 (108)	51 (86)	$< 10^{-5}$
≥ 4 positive	69 (24)	66 (21)	15 (50)	37 (95)	23 (84)	$< 10^{-5}$
≥ 50 yrs	67 (105)	61 (94)	30 (122)	51 (322)	50 (335)	$< 10^{-5}$
1-3 positive	77 (75)	71 (50)	41 (46)	63 (171)	65 (168)	$< 10^{-5}$
≥ 4 positive	42 (30)	48 (44)	24 (76)	35 (151)	36 (167)	$< 10^{-3}$

* Values = % disease-free patients (total No. of patients).

† I vs II vs III (Mantel-Cox test based on life table).

TABLE 2.—% disease-free survival at 4 yrs, by % dose level for PF (Method I)

Age and nodal status	Dose level *			Any dose * (689)	Control * (505)	P value†
	I (≥ 85%)	II (65%-84%)	III (< 65%)			
All patients	78 (311)	63 (166)	39 (207)	63	49	< 10 ⁻⁵
≤ 49 yrs	75 (120)	65 (71)	40 (89)	62 (284)	41 (170)	< 10 ⁻⁵
1-3 positive	89 (75)	74 (44)	65 (40)	77 (160)	56 (86)	0.009
≥ 4 positive	50 (45)	49 (27)	20 (49)	40 (124)	26 (84)	< 10 ⁻⁵
≥ 50 yrs	80 (191)	61 (95)	38 (118)	63 (405)	53 (335)	< 10 ⁻⁵
1-3 positive	83 (107)	73 (55)	44 (47)	72 (209)	68 (168)	< 10 ⁻⁵
≥ 4 positive	75 (84)	48 (40)	34 (71)	54 (196)	38 (167)	< 10 ⁻⁵

* Values = % disease-free patients (total No. of patients).

† I vs II vs III (Mantel-Cox test based on life table).

may be vividly demonstrated by examining the relationship between the dose of a placebo received and patient outcome (fig 1). Women receiving the greatest amount of placebo (Level I) had the best disease-free survival, while those getting < 65% of the placebo had a significantly poorer one.

With this method of dose determination, the longer the time of therapy specified by the protocol, the greater the magnitude of the bias. For example, a patient having a treatment failure any time within the first year of a prescribed 2 years of treatment cannot possibly receive Level I therapy; hence, the Level I group will contain no patients having treatment failures within the first year. If the protocol had stipulated that therapy be given for only 1 year instead of 2, patients who failed in the latter part of the first year may have received Level I therapy. The length of time that a patient must continue therapy to be classified in Level I is directly proportional to the prescribed length of the therapy.

Thus, for patients who had an early termination of therapy because of treatment failure or other events such as an early death, which precluded continuing therapy, it is inappropriate to base the maximum dose (denominator) on the full number of courses as defined by the protocol.

Method II

The following definition may seem to provide a logical method to correct for the bias observed with the first approach:

$$\text{amount of drug received (\%)} = \frac{\text{total of all drug received}}{\text{maximum protocol dose possible prior to treatment failure or death}} \times 100.$$

The results with this method differ from those noted when Method I was used. In general, patients receiving higher dose levels of P or PF demonstrated the poorest disease-free survival. With the use of P, patients receiving Levels II or III fared somewhat better than did those receiving the highest dose (Level I) (table 3). There was also a tendency for the PF-treated patients receiving Level III to have the best disease-free survival (table 4), even when Level I therapy was found to be beneficial. Thus, with the use of this approach for determining drug dose, it cannot be concluded that increasing amounts of drug are associated with better disease-free survival.

A major bias introduced with this type of analysis is that patients who failed early would be more likely to have received ≥ 85% of the protocol dose, since they would not yet have experienced toxicity sufficiently profound to have resulted in marked dose reductions. As patients progressively approach completion of therapy, the more likely it becomes that they have required a number of dose reductions because of episodes of toxicity, so that they receive a lesser percent of the protocol-prescribed dose. In addition, as the time of treatment progresses, the greater becomes the likelihood of noncompliance. This approach for obtaining the percent of drug received and for relating that percent to disease-free survival introduces a bias which is opposite in direction to that introduced by Method I. The use of a placebo group further illustrates the bias by this method, although the differences noted are not as strikingly significant because placebo does not produce toxicity (fig 1). Noncompliance, rather than toxicity, is the important factor introducing this bias when a placebo is employed.

Since neither of the two approaches results in an interpretable analysis, they are both inappropriate. The design of an appropriate analysis is hampered by a variety

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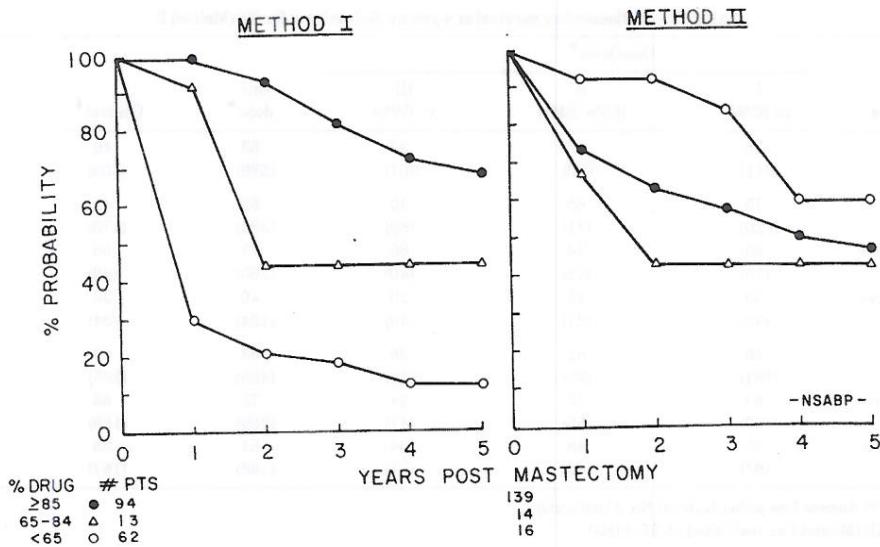


FIGURE 1.—% probability of disease-free survival related to dose level of placebo: Methods I and II.

of temporal factors which influence the amount of therapy received. That therapy is not administered as a single dose at one point in time and that one or more drugs are given repetitively during a prolonged time interval pose problems. During that period, physician or patient non-compliance, intercurrent disease, early treatment failure, early death, and other factors may interfere with the therapy as planned. The amount of toxicity requiring drug dose reduction also tends to be time-related in that it increases in frequency and degree as the time on therapy progresses.

Aside from the time-related factors, other factors such as age, degree of nodal involvement, and tumor characteristics, all of which influence the natural history (prognosis)

of the disease, may also affect the amount of drug received. For example, if it is decided at the start of a study to give older patients less of a therapeutic agent than is given to those who are younger because it is thought that they would be unable to tolerate as much drug, there will result a difference in that characteristic (age) between the groups receiving higher or lower doses. This type of confounding of prognostic factors must be considered in any analysis based upon such nonrandomized comparisons. Further, a difference in patient health status or other characteristics may covertly influence the physician to employ less than a "full" dose, leading to a selection bias in any dose-response comparison.

TABLE 3.—% disease-free survival at 5 yrs, by % dose level for P (Method II)

Age and nodal status	Dose level *			Any dose *	Control *	P value †
	I (> 85%)	II (65%-84%)	III (< 65%)			
All patients	47 (245)	59 (151)	55 (127)	51 (525)	46 (505)	0.005
≤ 49 yrs	46 (106)	75 (49)	46 (47)	52 (203)	37 (170)	0.006
1-3 positive	61 (56)	89 (28)	51 (23)	66 (108)	51 (86)	0.05
≥ 4 positive	31 (50)	56 (21)	41 (24)	37 (95)	23 (84)	0.03
≥ 50 yrs	48 (139)	50 (102)	60 (80)	51 (322)	50 (335)	0.06
1-3 positive	62 (85)	70 (53)	71 (33)	63 (171)	65 (168)	0.36
≥ 4 positive	24 (54)	29 (49)	52 (47)	35 (151)	36 (167)	0.001

* Values = % disease-free patients (total No. of patients).

† I vs II vs III (Mantel-Cox test based on life table).

TABLE 4.—% disease-free survival at 4 yrs, by % dose level for PF (Method II)

Age and nodal status	Dose level*			Any dose*	Control*	P value†
	I (≥ 85%)	II (65%-84%)	III (< 65%)			
All patients	60 (408)	65 (161)	70 (115)	63 (689)	49 (505)	0.01
≤ 49 yrs	57 (160)	67 (69)	70 (51)	62 (284)	41 (170)	0.02
1-3 positive	79 (84)	71 (46)	92 (29)	77 (160)	56 (86)	0.22
≥ 4 positive	31 (76)	58 (23)	44 (22)	40 (124)	26 (84)	0.04
≥ 50 yrs	63 (248)	64 (92)	71 (64)	63 (405)	53 (335)	0.28
1-3 positive	74 (121)	73 (55)	66 (33)	72 (209)	68 (168)	0.94
≥ 4 positive	51 (127)	54 (37)	75 (31)	54 (196)	38 (167)	0.11

* Values = % disease-free patients (total No. of patients).

† I vs II vs III (Mantel-Cox test based on life table).

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Method III

To surmount the problem caused by treatment failures occurring while patients are on therapy, the dose received up to a specific time may be related to the disease-free survival and survival subsequent to that time. If a specific time during therapy is selected for analysis of the amount of drug given, a problem arises in that the amount received after that time may also influence the end results. When a time is chosen at or after completion of the therapy that difficulty obviously does not occur, but another exists. A serious limitation of the method is that it utilizes only patients who have completed therapy without a treatment failure. As an example of this approach, disease-free survival was determined only in patients who had completed 2 years of PF therapy as stipulated by the protocol (fig 2). Patients who failed to receive the complete therapy because of treatment failure were not included. The disease-free survival was evaluated relative to the amount of drug received during the 2-year period. Variation in the amount of drug received failed to influence treatment failure either in all patients or in the two age groups. This was observed when either the melphalan or the 5-FU in the PF combination was evaluated separately or in combination. It is emphasized that these life-table plots do not present the overall response to the therapy but relate only to the disease status of patients subsequent to completion of 2 years of therapy.

While this method is not subject to the temporal biases in the first two methods, it provides a less than complete analysis of the results because of the omission of patients failing while receiving therapy. This is particularly serious, since the most striking differences in disease-free survival occur during that period of time.

Method IV

A method which is useful for considering the relationship between the amount of drug received and treatment failure includes information from all patients, even those who failed while on therapy. To evaluate the effectiveness of each dose level of chemotherapy received, the percent of protocol dose received is calculated for each patient to the time that a treatment failure occurs. With information on the distribution of doses received by all patients at risk of failing, it is possible to estimate a coefficient that represents a linear dose effect. This approach based upon the Cox model (7) also permits adjusting for other prognostic factors that may influence outcome. The methodology is well-described in recent statistical literature (8) and is employed extensively in the analyses of results from biomedical research. In our analyses the form of the regression model employed assumes a hazard function of the form:

$$\lambda(t) = \lambda_0(t) \exp [Z_1\beta_1 + Z_2\beta_2 + Z_3(t)\beta_3],$$

where $Z_1 = 0$ for age ≤ 49

= 1 for age ≥ 50

and $Z_2 = 0$ for 1-3 positive nodes

= 1 for ≥ 4 positive nodes

and $Z_3(t)$ is the cumulative dose at time t .

Note that with this method the amount of drug received is recalculated for each patient at the time of *each* treatment failure.

The analysis employed by us addresses several questions. Is there any evidence during the entire follow-up period that there is a relationship between the percent dose received and disease-free survival? Is the relationship between percent dose received and disease-free sur-

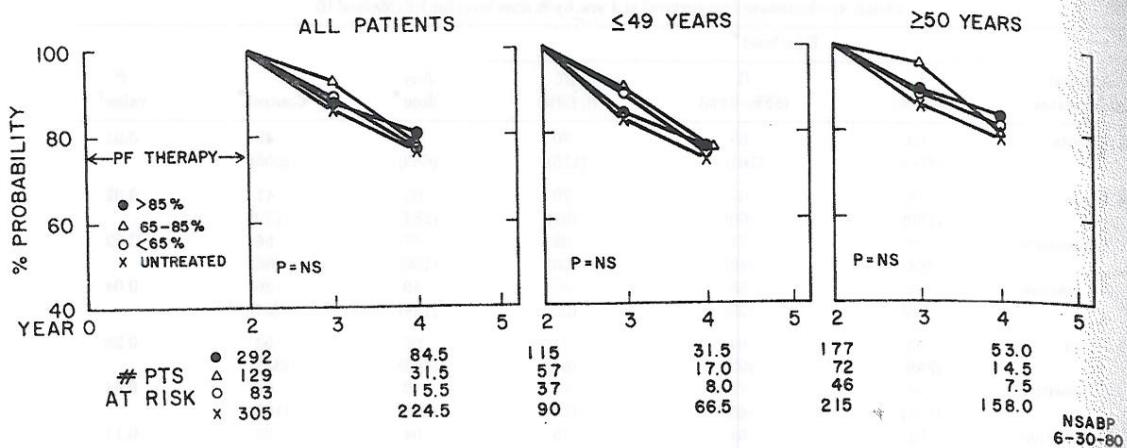


FIGURE 2.—Comparison of amount of therapy and disease-free survival subsequent to completion of therapy: PF.

vival most apparent during the time when chemotherapy is being received or only after the cessation of chemotherapy? Finally, does any reduction in dose immediately preceding a failure have an effect upon any apparent dose-response relationship? Information was sought to ascertain what influence the last course of therapy has in the analysis of the dose-response relationship. It was noted in some instances that patients who demonstrated a treatment failure did not receive their last scheduled course of therapy prior to the specific documentation of recurrent disease. For example, a patient presents for a scheduled course (dose) of chemotherapy and, as a result of clinical evaluation, it is decided to delay drug administration until it is determined whether or not the patient has a recurrence. If it is decided that she does have a treatment failure, the protocol therapy is discontinued. She may be documented as being noncompliant relative to her last course of therapy. To address this question, percent dose was based on all chemotherapy received up to 2 months prior to the documentation of a recurrence. If a dose-re-

sponse relationship is primarily related to the amount of therapy received in the period immediately preceding a treatment failure, evidence for a cause and effect relationship is tenuous since the dose reduction may be the result of the recurrence rather than vice versa.

The findings from two analyses are presented. In the first (table 5), the percent dose was calculated for each patient at risk based upon all courses the patient should have received up to the time at which a recurrence was documented. In the second (table 6), the percent dose was based on all courses the patients should have received up to 2 months prior to the documentation of a treatment failure. In all analyses, adjustment has been made for age (≤ 49 or ≥ 50 years) and number of positive nodes (1-3, 4-9, 10-14, or ≥ 15).

The results of the regression analysis relating the proportion of drug received to disease-free survival indicate that patients receiving PF therapy show some trend toward having a better disease-free survival during the 2 years of chemotherapy, if one considers all therapy up to

TABLE 5.—Cox regression analysis relating proportion of drug received to disease-free survival (overall)

Time interval	No. of patients	Coefficient	Standardized coefficient	P value *
Placebo patients				
All follow-up	168	-0.737	-1.947	0.05
0-2 yrs	168	-0.752	-1.499	0.14
> 2 yrs	102	-0.721	-0.721	0.19
PF patients				
All follow-up	648	-0.517	-1.759	0.08
0-2 yrs	648	-0.968	-2.425	0.015
> 2 yrs	478	-0.00007	-0.058	0.95
PMF patients				
All follow-up	329	-0.087	-0.258	0.80
0-2 yrs	329	-0.414	-0.414	0.67
> 2 yrs	240	-0.009	-0.009	0.99

* Two-sided.

TABLE 6.—Cox regression analysis relating proportion of drug received to disease-free survival
(time lag of 2 mos)

Time interval	No. of patients	Coefficient	Standardized coefficient	P value*
Placebo patients				
All follow-up	164	-0.269	-0.625	0.53
0-2 yrs	164	-0.331	-0.480	0.63
> 2 yrs	102	-0.719	-1.298	0.19
PF patients				
All follow-up	645	-0.171	-0.547	0.58
0-2 yrs	645	-0.342	-0.756	0.45
> 2 yrs	478	-0.019	-0.044	0.97
PMF patients				
All follow-up	324	0.097	0.275	0.78
0-2 yrs	324	0.230	0.399	0.70
> 2 yrs	235	0.00004	0.033	0.97

* Two-sided.

the time of treatment failure ($P = 0.02$) (table 5). For patients receiving PMF, no association between percent dose received and disease-free survival is evident. Similar evaluation of percent dose of placebo received suggests an association between dose and disease-free survival, with higher doses having a better result ($P = 0.05$). The strength of the association is almost the same for the period of therapy and following completion of therapy. When the last course of therapy prior to a treatment failure was disregarded in the analysis, the evidence for a dose-response relationship for PF was no longer significant ($P = 0.45$) (table 6). Similarly, when the last dose of placebo is disregarded, this association is also diminished for the period of time when patients are receiving placebo. The placebo findings indicate the need for caution in concluding a cause-effect relationship from observed associations between percent dose of chemotherapy and disease-free survival.

COMMENT

In view of the methodologic problems described, it is difficult to perceive how retrospective studies which purport to show a relationship between the amount of drug received and patient outcome can produce findings without statistical biases. Because such efforts are apt to have important biologic as well as clinical implications, they require critical evaluation prior to their unqualified acceptance. The difficulty, if not impossibility, of evaluating treatment efficacy after completion of a study by retrospectively delineating subgroups of patients according to amount of therapy received has also been demonstrated by findings from several clinical trials for diseases other than cancer. In one study evaluating the worth of tolbutamide therapy for diabetes (9) and in another assessing the efficacy of the lipid-influencing agent clofibrate for coronary heart disease (10), it was found that patients who took full or nearly full doses of those prolonged therapies fared better than did patients who

were less compliant. Similarly, however, control patients who complied with the protocols did better than control patients who were noncompliant. In both studies the compliant control and treated patients did equally well. Patients who were noncompliant in either study had similarly poor results, indicating that noncompliers differ from compliers for reasons unrelated to the therapeutic effect. Thus, positive dose-response relationships must be interpreted with caution.

The present report demonstrates that it is difficult to relate total dose to results from initiation of therapy onward. It is not clear how the problem was overcome in studies where an attempt was made to correlate the amount of drug received and patient outcome (1,3). The methodology presented in the CMF study indicates that the drug dose received by patients with treatment failures was based on the number of courses given to the time of treatment failure (1). Utilizing a similar approach with our data (Method II), an opposite relationship between dose and response to that obtained in the CMF analyses was observed. The results in that study generally resemble the uniformly positive findings that we obtained using the first method for defining dose. The comparison of patients who received therapies for different durations (eg, six or 12 cycles of CMF) also presents methodologic difficulties, since percent dose received by patients failing during therapy will be related to the prescribed length of the therapy. The length of the therapy will affect the end results within dose groups for reasons unrelated to the amount of drug received, as demonstrated by us with placebo on Protocol B-05. The use of Method I (or an equivalent method) is implied in the comparison of six to 12 cycles of CMF, as well as by the total absence of treatment failures during the 1 year of therapy for patients receiving $\geq 85\%$ of the intended dose of CMF. Hence, it is impossible for the group receiving Level I therapy for 1 year to have a poorer outcome during that year.

Findings from a study by the Southwest Oncology Co-

operative Group employing combination chemotherapy (CMFVP) versus melphalan also point to the dilemma. Results from that investigation (3) failed to indicate any clear relation between the percent of dose received and patient outcome. That comparison was subjected to the same biases which have been described for our Method I. Moreover, there is an additional problem in that the different regimens were administered for a different length of time. The amount of bias is thus different for the different therapies.

Another concern relates to the total confounding of age with the dose administered to older patients. Previous analyses of data have indicated that there is a differential response by age; younger women do better than the older women. If the treatment effect is age-related and drug dose is differentially administered according to age, then stratifying by age or dose accomplishes essentially the same result. Since there is a relationship to age, there will appear to be a relationship to dose. Statistical analysis cannot compensate for this type of total confounding.

This report is presented to emphasize that retrospective analyses, even when directed toward overcoming the many potential biases, must be regarded with caution. Results from them must be considered exploratory and not conclusive in nature. In any positive dose-response relationship, it is difficult, if not impossible, to distinguish cause from effect. In other words, do patients complying and receiving full doses do well, or do patients doing well comply and receive full doses? Prospective trials a priori designed to take into account the biases must then be carried out to obtain definitive findings.

REFERENCES

1. BONADONNA G, and VALAGUSSA P. Dose-response effect of adjuvant chemotherapy in breast cancer. *N Engl J Med* 343:10-15, 1981.
 2. SENN H, JUNGI WF, and AMGWERD R. Chemo (immune) therapy with LMF + BCG in node-negative and node-positive breast cancer. In *Adjuvant Therapy of Cancer III* (Salmon SE, and Jones SE, eds). New York, Grune & Stratton, 1981, pp 385-393.
 3. GLUCKSBERG H, RIVKIN SE, RASMUSSEN S, ET AL. Combination chemotherapy (CMFVP) versus L-phenylalanine mustard (L-PAM) for operable breast cancer with positive axillary nodes. *Cancer* 50:423-434, 1982.
 4. TORMEY DC, WEINBERG VE, HOLLAND JF, ET AL. A randomized trial of five and three drug chemotherapy and chemo-immunotherapy in women with operable node positive breast cancer. *J Clin Oncol* 1:138-145, 1983.
 5. FISHER B, REDMOND C, FISHER ER, ET AL. The contribution of recent NSABP clinical trials of primary breast cancer therapy to an understanding of tumor biology—an overview of findings. *Cancer* 46:1009-1025, 1980.
 6. FISHER B, REDMOND C, WOLMARK N, ET AL. Disease-free survival at intervals during and following completion of adjuvant chemotherapy: the NSABP experience from three breast cancer protocols. *Cancer* 48:1273-1280, 1981.
 7. COX DR. Regression models and life tables. *J R Stat Soc B* 34:184-220, 1972.
 8. KALBFLEISCH J, and PRENTICE R. *The Statistical Analysis of Failure Time Data*. New York, John Wiley & Sons, 1980.
 9. CORNFIELD J. The University Group Diabetes Program—a further statistical analysis of the mortality findings. *JAMA* 217:1676-1687, 1971.
 10. THE CORONARY DRUG PROJECT RESEARCH GROUP. Influence of adherence to treatment and response of cholesterol on mortality in the coronary drug project. *N Engl J Med* 303:1038-1041, 1980.