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Calculation of received dose intensity for combinations of drugs using small-cell lung carcinoma treatment regimens as examples

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Summary. Programs are presented for the calculation of received dose intensity in combination chemotherapy regimens. These provide methods for determining the final dose intensity, the mean cumulative dose intensity together with its standard error, and other tabular and graphic summaries. Two ways of dividing patients into high and low received-dose-intensity groups are proposed. Methods are illustrated using data from Mid-Atlantic Oncology Program (MAOP) 2183, a phase III evaluation of a six-drug alternating combination vs a three-drug "standard" combination treatment for extensive small-cell lung cancer. Comparisons of received dose intensity with demographic and outcome variables are presented.

Introduction

Dose intensity has been reported to be associated with outcome in retrospective studies [6, 7, 13, 14, 16, 18, 19]. One prospective study found that higher dosing resulted in improved survival and in a better quality of life [26]. Dose intensity is believed to be an important determinant for cure in aggressive lymphomas [7, 18] and germ-cell tumors [6, 22]. Baar and Tannock [2] have suggested that all clinical studies should contain analyses of dose intensity. If so, it would be desirable to establish a standard way of reporting received dose intensity just as standard methods of reporting toxicity and response have been developed. Noting differences in the existing methods for the calculation of received dose intensity, Hryniuk and Goodyear [15] suggested a method that avoids some of the more obvious biases that can result from their use.

In the present report, this method has been expanded and modified so as to make it applicable to a wider range of data sets. Two combination chemotherapy regimens are analyzed in which considerable data censoring has occurred. These illustrate problems that may not have been fully appreciated from previous reports. Criteria are also provided for the division of patients into high and low received-dose-intensity groups for statistical comparisons.

Several problems arise with the use and interpretation of dose-intensity measurements:

1. Scheduled (intended or projected) dose intensity may be confused with received (actual or delivered) dose intensity. Scheduled dose intensity has been the principal topic of a number of publications involving interprotocol comparisons [7, 14, 16, 19], whereas other authors have calculated received dose intensity [6, 18, 20, 21]. Received dose intensity is more subject to inadvertent bias since schedule and dose adjustments are made after treatment assignment. Scheduled dose intensity may not accurately describe the doses actually given. As a result, conclusions related to scheduled dose intensity may not apply to received dose intensity, and vice versa.

2. The expression of dose intensity frequently involves conversion to a percentage or fraction of a standard. For scheduled dose intensity, either this standard is selected empirically from the regimens being compared and is usually the most dose-intense [14, 19] or a hypothetical standard is constructed [7]. For received dose intensity, the standard used is the scheduled dose intensity of each regimen. Other investigators have applied an external standard such as a commonly used regimen [18]. Obviously, the standard selected influences the result and can lead to problems in the comparison of any results or conclusions reported.

3. Dose-intensity calculations have largely ignored possible variations in effectiveness for different treatment schedules (single dose, multiple dose, and infusions, among others) of a drug or regimen [8]. However, in defense of this practice, it does seem that in most cases, the degree of influence exerted on the outcome using different

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schedules of treatment is of a lesser magnitude than that obtained via dose variation.

4. Underlying dose intensity is the basis of a dose response. The dose-response relationships for most human neoplasms are poorly understood. Animal studies demonstrate that dose responses differ between different tumor types [11] and among various end points (e.g., tumor shrinkage and survival) [3]. There is a limit to the statement "the more, the better" with regard to survival, as toxicity intervenes at some point and higher dosing results in shorter survival. Optimal dosing is an important concept derived from animal studies that requires adequate inspection of the dose response for its determination. Dose responses are typically non-linear (especially in the absence of scale transformation); consequently, studies examining different regions of a dose response can easily report contradictory results [11]. This is illustrated by a randomized study in testicular cancer that compared the administration of cisplatin at a full dose vs a double dose in a cisplatin, etoposide, and bleomycin regimen [23]. This study showed no benefit for the high-dose arm in terms of response, disease-free survival, or overall survival, indicating a flat response over the dose levels explored. The results would likely have been different had the full dose been compared with some reduced and less effective dose of cisplatin in this regimen.

5. Sicker patients are more likely to have their dose reduced or delayed. This introduces a bias that may produce an association between received dose intensity and outcome that is not due to dose-response effects [1, 4].

6. The relative contribution of individual drugs in a combination is not known, which leads to arbitrary decisions in the computation of dose intensity when multiple drugs are involved [6, 7, 14, 17, 21].

For all of these reasons, the standardization of methodology for dose-intensity calculation is desirable.

Patients and methods

Treatment protocol. Treatment data from Mid-Atlantic Oncology Program (MAOP) 2183 are used in the present report to demonstrate the calculation of received dose intensity. In MAOP 2183, patients were randomized on a 1 : 1 basis to receive either cyclophosphamide/doxorubicin/vincristine (CAV) or the regimen methotrexate/etoposide/cisplatin (MEP) alternating with CAV. In the CAV regimen, which was given every 3 weeks, cyclophosphamide was injected as an i. v. bolus on day 1 at a dose of 1200 mg/m^2; doxorubicin, at a dose of 45 mg/m^2; and vincristine, at a dose of 1.4 mg/m^2 (maximal dose, 2 mg). The MEP regimen consisted of i. v. bolus injection of 40 mg/m^2 methotrexate on day 1, of 100 mg/m^2 etoposide on days 1–3, and of 100 mg/m^2 cisplatin on day 3. After 3 weeks, CAV was given as described above, and then treatment was alternated between MEP and CAV at 3-week intervals unless toxicity required modification or discontinuation of the treatment.

Treatment was delayed by 1 week if the WBC at the time of scheduled treatment was <4000/mm^3, if the platelet count was <100,000/mm^3, or if the creatinine value was >1.5 mg/dl. If after 1 week these laboratory values had remained abnormal, dose modification was undertaken. The original protocol called for treatment until progression of disease or for 1 year. However, as evidence emerged that shorter therapy was equally effective, treatment beyond month 6 was made optional. A schema of the treatment protocol is shown in Fig. 1.

MAOP 2183 data were collected by two statistical centers using different formats. Initially, the treatment data consisted of the total cumulative doses of drugs, the number of cycles given, and the dates of patient registration and final treatment. Later, the dates and the amounts of drugs given for each treatment were recorded. Data collected in these two ways are labeled record group 1 and record group 2, respectively, in the present report and are used to illustrate the possible calculations for each type of data.

Week 1	Week 4	Week 7	Week 10	Week 13	Week 16
Day	Day	Day	Day	Day	Day
1,2,3	22	43,44,45	64	85,86,87	106
C	C	C	C	C	C
A	A	A	A	A	A
V	V	V	V	V	V
M	C	M	C	M	C
E,E,E	A	E, E, E	A	E, E, E	A
P	V	P	V	P	V

Fig. 1. Schema for MAOP 2183, showing the scheduled dose for 6 cycles of CAV and 3 cycles of MEP/CAV and the treatment schedule for 126 days. Patients who remained on treatment for a longer period received repeated cycles of the same drugs at the same doses

C = Cytoxan, 1200 mg/m^2
A = Adriamycin, 45 mg/m^2
V = Vincristine, 1.4 mg/m^2 (max. 2 mg)
M = Methotrexate, 40 mg/m^2
E = Etoposide, 100 mg/m^2
P = Cisplatin, 100 mg/m^2

A total of 170 patients were enrolled on MAOP 2183, with 85 being randomized to each treatment arm. The results of the study have been published elsewhere [27]. Complete treatment information was collected for 142 patients (84%), 47 in record group 1 and 92 in record group 2. Three patients were known to have received no protocol treatment. The dose-intensity-related issues reported in this paper were analyzed retrospectively.

Definitions. The following terms are defined so as to clarify the text and enhance the understanding of the calculations. *Scheduled dose intensity* is based on doses planned for a regimen, whereas *received dose intensity* is calculated from the amount of drug(s) actually given. The topic of this paper is received dose intensity. *Dose strength* is used to define the fraction of the scheduled or full dose that was given. *Delay factor* is the component of the dose intensity resulting from delays in treatment as compared with the intended regimen. For example, if a treatment were given every 4 weeks instead of every 3 weeks, the delay factor would be 0.75. *Relative* as applied to dose intensity, dose strength, or delay factor refers to a value reported as a fraction or percentage of a standard. *Combination* used in reference to dose intensity, dose strength, or delay factor indicates a computation involving multiple drugs. Usually, the relative dose intensities of all drugs are averaged to obtain an unweighted dose intensity for the combination. Medians or geometric means may also be reported. Calculation of dose intensity requires the use of both dose and time and has been classically defined as the amount of drug given weekly in milligrams per square meter. In the present report, dose intensity is calculated by multiplying the dose strength by the delay factor. The results do not differ substantively from those obtained using the classic method inasmuch as reporting of any combination dose intensity requires a conversion to relative values.

The separate components dose intensity, dose strength, and delay factor are included in the computations because dose intensity can be diminished either by a reduction in the dose or a delay in treatment, resulting in possible differences in the therapeutic effect. Therefore, it is desirable to observe and report the values for the two components independently.

Since dose intensity changes with time, it is necessary to calculate a cumulative dose intensity. *Final* is used to identify values associated with calculations involving the total treatment period and gives a single value for each patient. The use of both methods provides adequate information

and avoids the necessity of arbitrarily selecting a set number of cycles or a cutoff time for inclusion in the analysis.

Statistical procedures. Three SAS (SAS Institute Inc., Cary, N. C.) programs were written for the calculation of dose intensity (obtainable from the Mid-Atlantic Oncology Program, 8811 Coleville Road, Suite 111, Silver Spring, MD 20901, USA). The first is a dose-intensity utility program (DIUP) to assist in cleaning up the data. The second, for received-dose-intensity calculation (DIFINAL), calculates the final dose intensity for the varying time during which patients are under treatment and outputs tabular and graphic summaries of values for individual patients and group values along with mean and median dose intensities for each drug or for the combined drugs. Patients are then divided into high and low received-dose-intensity groups by the regression method described below so as to enable comparisons with other variables. The third program (DICUM) calculates a mean cumulative received-dose-intensity (±SE) for each day through 180 days on study. Patients can be separated into two dose-intensity groups (high and low) on any day or days simply by dividing those whose values lie above the mean from those whose values fall below the mean. For all comparisons, the Mantel-Haenszel chi-square test is used.

The programs were run on an IBM 3081Q system taking <1 min CPU and <4000 lines of print; they can also be run on PC SAS Version 6.06 or earlier versions. All programs can be run on <640 kilobytes of random access memory (RAM) except Proc GLM, which is used for the separation of patients into high and low dose-intensity groups in the DIFINAL program and requires a 386 or 486 computer equipped with DOS 5.0 and up to 2 megabytes of expanded memory.

Final dose intensity (FDI) was calculated using the following formula:

$$\text{FDI} = \frac{n_c t_c}{t} \sum_{k=1}^{n_d} \sum_{j=1}^{n_{tk}} \frac{R_{jk}}{n_c n_d S_k}$$

where n_c represents the number of treatment cycles received; t_c represents the cycle time; t indicates the treatment time, representing the actual duration of treatment extended to the time at which the next cycle would have been due for reasons discussed below; R_{jk} represents the received dose of drug k by the individual at the jth treatment, where $k = 1,2,..n_d$ and $j = 1,2,..n_{tk}$, n_d being the number of drugs received by the individual and n_{tk}, the number of treatments with drug k received by the individual; and S_k indicates the scheduled or full dose of drug k for each cycle. The expression $n_c t_c/t$ represents the delay factor, and the double-summation term computes the dose strength. The n_c values cancel and are needed only for individual calculations of the delay factor and the dose strength. It should also be noted that $n_{tk} \geq n_c$, since the number of treatments per cycle with drug k may be multiple.

Cumulative dose intensity (CDI) is calculated using a similar formula:

$$\text{CDI} = \frac{n_c}{C} \sum_{k=1}^{n_d} \sum_{j=1}^{n_{tk}} \frac{R_{jk}}{n_c n_d S_k}$$

where C represents the cycle number due; the other expressions are defined as noted above. The two formulae differ only in the expression used to calculate the delay factor, and these become equivalent for large values of C ($t_c/t \sim 1/C$). In both of the formulae, the doses have to be expressed in the same units (mg/m^2), as does time (weeks or days).

A different formula is required for the calculation of cumulative dose intensity because of problems in the definition of the treatment time when the FDI formula is used. Our definition is that treatment time has a single value for each patient. If the definition involves the greater of the last treatment date plus the cycle time or the day of study, values greater than the FDI are usually obtained and average values over days or over patients are substantially higher. This is illustrated in Table 1. The CDI formula tends to yield comparable results with lengthening time.

The body surface area was recalculated for each patient using the method of DuBois and DuBois [9]. If height was missing, an average height of 67 inches for men or 62 inches for women was assumed; this was necessary in 7 cases. One patient whose weight was missing was assigned a body-surface-area value of 1.75 m^2, which corresponded to the initial dose given. More sophisticated statistical methods are available that can supply missing data, or, optionally, such patients may be excluded. However, exclusion of patients should be avoided, as it invariably leads to the introduction of bias.

Table 1. Daily cumulative-dose-intensity calculations for a hypothetical subject receiving a full dose on day 1 and a full dose on day 29, corresponding to a 1-week delay, using the (FDI) formula and the (CDI) formula

Day	FDI	CDI
1–21	1.00	1.00
22	0.95	0.50
23	0.91	0.50
24	0.88	0.50
25	0.84	0.50
26	0.81	0.50
27	0.78	0.50
28	0.75	0.50
29–42	1.00	1.00
43	0.98	0.67
44	0.95	0.67
45	0.93	0.67
46	0.91	0.67
47	0.89	0.67
48	0.88	0.67
49	0.86	0.67
Average	0.97	0.88

The true FDI is 0.86, the value shown for day 49. After the second cycle is due (day 22), the daily average dose intensity for a group of patients would be misleading if it were calculated using the FDI formula. Dose delays in some patients cause cycles to become staggered, and the average CDI yields group values for each day of study that more nearly approximate the true values

Decisions regarding the dose-intensity calculation include the following:

1. Weighting considerations. Not all drugs contribute equally to the effectiveness of a combination. For example, it could be argued that the six-drug regimen adds nothing beyond the results obtained using etoposide/cisplatin [10, 24]. Also, drugs given early during the course of treatment undoubtedly have more effect than do those given at a later time. However, a uniform weighting scheme was selected because the precise contribution of each drug or of the early vs late administration of drugs is not known. Even so, some weighting occurs in the cumulative-dose-intensity calculation. The average cumulative dose intensity (and standard error) is calculated for each day using all patients remaining on study on that day. Thus, patients treated over longer periods contribute more to the statistics generated.

2. Definition of the treatment-time (t) parameter. The question as to how the time parameter should be defined is of critical importance since dose intensity is defined as the dose per unit of time. Patients who are scheduled to receive a full dose over a 3-week cycle of treatment but die at the end of week 1 are off protocol, but if that date is used for the calculation of relative dose intensity, a value of 3.0 is obtained. One might therefore find that high dose intensity is associated with short survival. This dilemma is avoided by extending the treatment period to the time at which the next treatment is due, as proposed by Hryniuk and Goodyear [15]. In the case of the example cited above, the treatment time would be 3 weeks, or 2 weeks past the date of death. This maneuver does not entirely correct the problem of high dose intensity for patients who die early, since some of these individuals, had they lived, would have required treatment delays. Coppin [5] explained treatment time in a different way, but the resulting value for this parameter was identical to that obtained using the method of Hryniuk and Goodyear.

If an arbitrary cutoff point for treatment time is specified for all patients, regardless of whether they are on treatment, long treatment times and low dose intensities are recorded for subjects who drop out as compared with the values obtained using the method of Hryniuk and

Goodyear. Dropouts are usually attributable to mortality or to progressive disease. This assures the association of low dose intensity with an undesirable outcome.

Other methods have been used that result in treatment times shorter than those obtained by the method of Hryniuk and Goodyear. Skipper [25] ignores any extension of the time beyond the day on which the last dose is given, which leads to high dose-intensity calculations for animals receiving a single dose or undergoing a short course of treatment. Other authors have used Skipper's method or other variations to determine the treatment time [1, 6, 12, 21]. Thus, different conventions are recorded in the literature that seriously affect the conclusions that have been drawn.

3. Vincristine dose intensity. Vincristine was given at a dose of 1.4 mg/m^2 (maximal dose, 2 mg). If dose intensity is calculated without regard to the maximal cutoff, reduced dose intensity is obtained for all larger patients. If 2 mg is counted as a dose strength of 1.0, then all large patients usually achieve a dose intensity of 1.0 unless dose delays are necessary, although they may not have been treated as intensively as smaller patients.

The latter method of calculating the dose intensity for vincristine was selected for this report. Klasa et al. [17] found it impossible to calculate the vincristine scheduled dose intensity for use in a meta-analysis. Other authors have had difficulties with the computation of vincristine dose intensity [6, 21].

4. Methotrexate dose intensity. Although no problem was experienced in the present analysis, other authors have encountered difficulty when leucovorin is used with high dose methotrexate [6, 7]. Arbitrary decisions have been made because of the attenuation of drug efficacy by the administration of an agent to reduce hematologic toxicity.

5. Division of patients into groups according to the level of dose intensity simplifies statistical testing and the presentation of data such as survival by dose intensity. No optimal method for assigning subjects to high and low dose-intensity groups is known. Each patient achieves different dose intensities over different periods during treatment, which are usually greater during the early stage of therapy. The phenomenon of dose intensity fade occurs in patients who have been under treatment for longer periods, as such individuals are more likely to require delays or dose reductions that result in lower dose intensity [5]. The FDI determined using the final dose-intensity program is the only value that can be calculated for patients whose data place them in record group 1. In small-cell lung cancer, of which a number of patients die during treatment, the correlation of survival with FDI shows that high dose intensity is associated with short survival due to the dose-fade phenomenon. This problem is less apparent when most of the patients live to complete their course of treatment or when a short treatment course is analyzed. For circumvention of this problem, a regression line can be calculated from the data used to generate Fig. 2, which represents a plot of dose intensity by treatment time. Patients whose values lie above the regression line represent the high dose-intensity group, and those whose values fall below the line represent the low dose-intensity group.

For the cumulative dose-intensity program, which evaluates only patients for whom all daily doses have been recorded, the mean dose intensity by day on treatment through 180 days is calculated. Any day could be picked for division of subjects into two groups, depending on whether their dose intensity is greater or less than the median value. This report uses day 30, since patients should have received two cycles of CAV or one cycle of MEP/CAV by this time, and survival results for most patients were unknown. Patients are equally divided into two groups: those whose values are above the median 30-day dose intensity and those whose values are below this cutoff point.

6. Median or mean dose intensity. Median values are less susceptible than mean values to fluctuation due to errors in the data, but both mean and median values are reported herein. Mean values are used for graphing, mainly because standard errors can be easily calculated. In this way, information is provided on the variability in the data without the need to present the dose-intensity curve for each individual. An alternative method would be to present the median value along with 25%–75% ranges. Previously, plots of cumulative dose or cumulative dose intensity have used individual subject plots to indicate variability [5, 20].

7. What should be done with patients who receive no treatment? In this study, 3 of the 170 subjects entered received no protocol treatment. Whether they received other treatment is unknown. As neither treatment time nor dose intensity can be calculated without detailed information on at least one treatment, these three patients were excluded from the analysis. Inclusion of these subjects as zero dose-intensity values would affect the mean and median results.

8. Round-off convention. Numbers were rounded off to two decimal places.

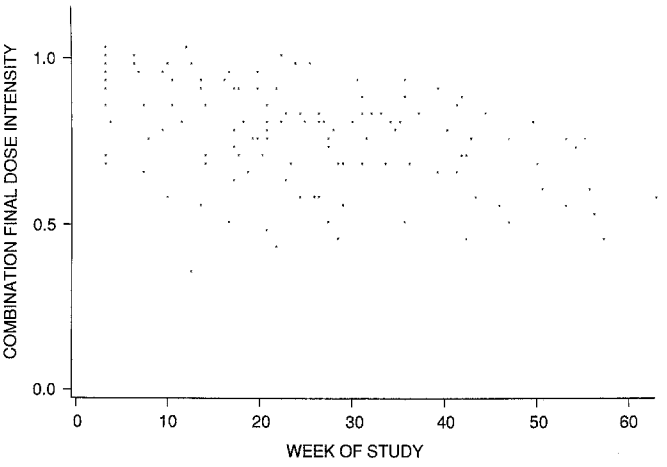

Fig. 2. Final combination received dose intensity according to duration of treatment. Each point represents one patient. The time parameter (*abscissa*) represents the specifically defined treatment period used for dose-intensity calculation. For any patient receiving treatment, this cannot be less than the time involved in one cycle (3 weks in this study)

Results

FDI information for MAOP 2183 is summarized in Table 2. Patients receiving CAV were on study for a mean of 18.8 ± 15.6 weeks at a mean final combination dose intensity of 0.80 ± 0.17, whereas those receiving the alternating regimen were on treatment for 24.5 ± 17.3 weeks at a mean final combination dose intensity of 0.75 ± 0.16. Figure 2 shows the final combination dose intensity by treatment time. By definition, no treatment time was less than the cycle duration of 3 weeks. The program also prints individual dose-intensity plots for each drug in the combination. Total doses of each drug by dose per week are plotted as previously published by Coppin [5]. Results by patient for dose strength, delay factor, received dose intensity for each drug, and overall values are shown as well as the total cumulative dose and the dose in milligrams per square meter per week for each drug. The program also computes dose intensity and other statistics for individual drugs and for combined drugs by regimen as listed in Table 2.

The mean cumulative combination dose intensity ($\pm$SE) is plotted in Fig. 3 and 4. The ordinate represents the dose intensity in Fig. 3, whereas in Fig. 4 it indicates the cumulative dose, both being expressed in units (all drugs combined) whereby a value of 1.0 represents the full dose. These plots are analogous to those presented by Coppin [5], except that we used standard errors instead of plotting individual dose intensities on the same graph.

In the FDI analysis, 57 patients in the low dose-intensity group achieved a median dose intensity of 0.67 (range, 0.07–0.85; median time, 20.14 weeks) and 82 patients in

Table 2. Summary of the final received dose intensity

Treatment		Mean dose intensity (±SE)	Median dose intensity	Mean/median dose strength	Mean/median delay factor
All patients together:					
Cyclophosphamide ($n = 131$)[a]		0.75 ± 0.19	0.78	0.91/0.94	0.85/0.90
Doxorubicin ($n = 131$)[a]		0.75 ± 0.19	0.77	0.90/0.94	0.85/0.90
Vincristine ($n = 131$)[a]		0.79 ± 0.19	0.83	0.96/1.00	0.85/0.90
Methotrexate ($n = 68$)		0.77 ± 0.17	0.79	0.97/0.96	0.81/0.86
Etoposide ($n = 68$)		0.77 ± 0.17	0.81	0.97/0.96	0.81/0.86
Cisplatin ($n = 67$)		0.73 ± 0.19	0.77	0.91/0.93	0.81/0.86
All combined ($n = 139$)		0.77 ± 0.17	0.82	0.92/0.93	0.85/0.90
By regimen:					
Cyclophosphamide	A	0.79 ± 0.20	0.83	0.89/0.95	0.89/0.94
(A, $n = 71$; B, $n = 60$)[a]	B	0.71 ± 0.18	0.76	0.92/0.93	0.81/0.86
Doxorubicin	A	0.78 ± 0.19	0.81	0.89/0.94	0.89/0.94
(A, $n = 71$; B, $n = 60$)[a]	B	0.72 ± 0.18	0.75	0.93/0.94	0.81/0.86
Vincristine	A	0.82 ± 0.19	0.91	0.93/1.00	0.89/0.94
(A, $n = 71$; B, $n = 60$)[a]	B	0.76 ± 0.18	0.80	0.99/1.00	0.81/0.86
Methotrexate	A	–	–	–	–
(A, $n = 0$; B, $n = 68$)	B	0.77 ± 0.17	0.79	0.97/0.96	0.81/0.86
Etoposide	A	–	–	–	–
(A, $n = 0$; B, $n = 68$)	B	0.77 ± 0.17	0.81	0.97/0.96	0.81/0.86
Cisplatin	A	–	–	–	–
(A, $n = 0$; B, $n = 67$)	B	0.73 ± 0.19	0.77	0.91/0.93	0.81/0.86
All combined	A	0.80 ± 0.17	0.82	0.90/0.94	0.89/0.94
(A, $n = 71$; B, $n = 68$)	B	0.75 ± 0.16	0.78	0.95/0.93	0.81/0.86)

Doses are reported as a fraction of the scheduled dose. A, CAV regimen; B, MEP/CAV regimen

Treatment cycles: A, 5.68 ± 4.16 (median number of 3-week cycles, 5); B, 3.25 ± 1.96 (median number of 6-week cycles, 3). Treatment duration: A, 18.75 ± 15.58 weeks (median, 15.71 weeks); B, 24.45 ± 17.28 weeks (median, 22.57 weeks)

[a] Eight patients died or refused treatment before the first CAV treatment was due

the high dose-intensity group attained a median dose intensity of 0.89 (range, 0.58–1.03; median time, 20.21 weeks). Initially, 92 patients were eligible for the cumulative dose-intensity analysis, but only 69 had remained on study by day 30. The median 30-day dose intensity for 34 patients in the low dose-intensity group was 0.93 (range, 0.33–0.98), and that in the high dose-intensity group of 35 patients was 1.00 (range, 0.98–1.07). The associations between dose intensity and other variables are given in Table 3.

The robustness of the statistical comparisons was checked by repeating the analysis using the natural logarithm of the received dose intensity. This maneuver did not change the correlation of the groups for 30-day cumulative dose intensity. For FDI, no new variable showed a loss or gain for P values of <0.05. Due to the phenomenon of dose fade, a linear relationship between time and dose intensity may not be appropriate. Accordingly, a model allowing for curvature was tested that produced only minor changes in the P values of the correlations. Neither of these maneuvers improved the fit to the data. These results indicate that the statistical test used is suitably robust.

Discussion

It is clear that methods for the calculation of dose intensity are not uniform. Authors have described their methods in words [14, 15], have used partial formulas [21], plotted the cumulative dose by time and used a regression line through the points [20], or have measured the slope of the plot of the mean cumulative dose [5] as the procedure for computing dose intensity. Certain arbitrary assignments such as the period of treatment analyzed, the selection of a standard for comparisons, the choice of treatment time (t), the

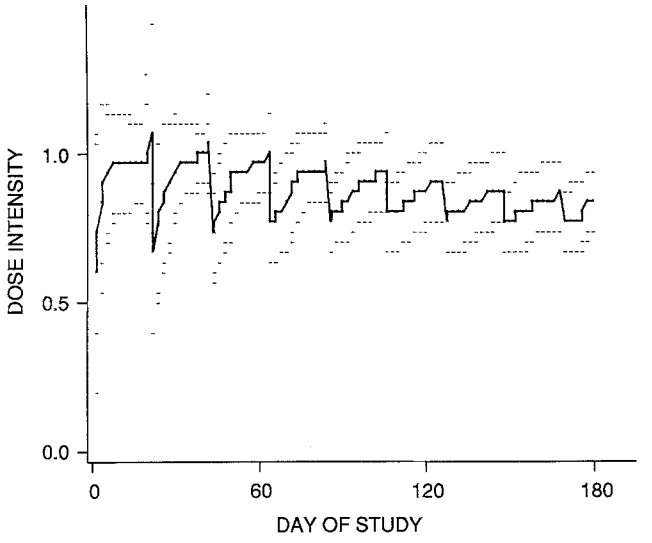

Fig. 3. Mean cumulative combination received dose intensity (±SE) acording to time. The actual computer output is shown, with a line being added (for emphasis) to join the mean values for dose intensity obtained on each day of study. Every 21 days the denominator changes when a new treatment becomes due, which accounts for the irregularities in the line

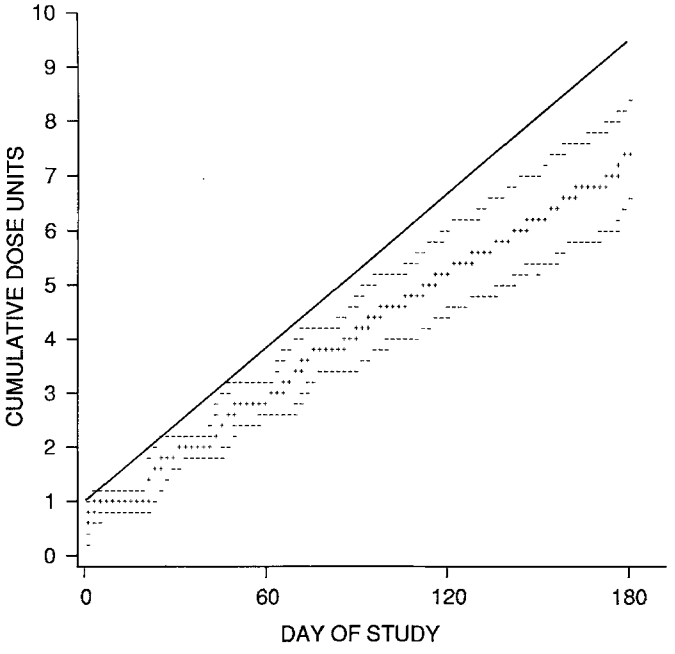

Fig. 4. Mean cumulative combination dose (±SE) according to time. The actual computer output is shown. The cumulative dose increases with each treatment; plotting of these values produces a stair-step pattern. The *solid line* represents the scheduled cumulative dose, the line being drawn through points indicating the 1st day of each treatment cycle. Plotting of the daily scheduled dose would also produce a stair-step pattern. Dose fade is indicated by the progressive separation of the median cumulative received dose from the cumulative scheduled dose

Table 3. Association of dose intensity with other variables

Variable	Dose-intensity group	
	Cumulative, day 30	Final
Ambulatory status	0.593	0.514
Sex	0.943	0.324
Race	0.302	0.013*
Age group[a]	0.345	0.406
Bone metastases	0.733	0.021*
Marrow metastases	0.309	0.351
Brain metastases	0.593	0.071**
Liver metastases	0.180	0.891
Lung metastases	0.961	0.672
Node metastases	0.888	0.638
Number of sites of metastases	0.266	0.500
Size[b]	0.607	0.692
Pathologic subtype[c]	0.138**	0.521
Regimen	0.728	0.467
Weight-loss group[d]	0.958	0.252
WBC	0.400	0.020*
Platelet count	0.163	0.451
Vomiting	1.000	0.911
Diarrhea	0.317	0.808
Stomatitis	0.154	0.684
Infection	1.000	0.719
GU toxicity	1.000	0.345
Neurotoxicity	1.000	0.881
Response	0.136**	0.065**
Time to progression	0.506	0.094**
Survival[e]	0.733	0.558
Institution[f]	0.636	0.443

Data represent P values (chi-square test) >observed values. Metastases to the various organs were recorded as being either absent or present based on registration data. Toxicities, based on common Cooperative Group criteria grade, were dichotomized for analysis as being moderate or less vs severe or greater

* $P \leq 0.05$, ** $P = 0.05 - 0.15$

[a] ≤60 years in one group, >60 years in the other

[b] ≤1.75 m^2 in one group, >1.75 m^2 in the other

[c] Cell type classified as small-cell undifferentiated, intermediate, or mixed

[d] ≤10% in one group, >10% in the other

[e] ≤8 months in one group, >8 months in the other

[f] Medical centers vs private practice

exclusion of patients, and weighting (whether inadvertent or not) have been criticized [4, 8, 11]. In presenting a method for the calculation of FDI, it is important that arbitrary decisions made after the fact be avoided as far as possible. Thus, the internal standard advocated is scheduled dose intensity, which allows no retrospective choice and avoids the criticisms directed at external standards such as the subjective choices for comparison of the activities of similar drugs or the variations in drug scheduling of the external standard regimen with the treatment regimen. Additionally, the result, reported as a fraction or percentage of the intended dose, is the finding that generally appears in articles reporting on received dose intensity. The use of all dose information allows no retrospective choice as to the interval to be analyzed; all treated patients can be included, even if the only parameters known are the total cumulative dose and the treatment time. The avoidance of weighting, although it may be justified, seems appropriate at present. However, the FDI value ob-

tained does not provide information as to how the treatment may have changed with time. Since such information is important, the method of calculating cumulative dose intensity is also presented.

In terms of the results presented in the tables and figures, it is noteworthy that very little initial variation in dosing occurred for protocol 2183; that is, the doctors could give protocol doses quite accurately. Consequently, nonuniform weighting of the drugs would have made little difference in dose intensity results. Delays in treatment were probably mainly responsible for the lower dose intensity of the alternating regimen as well as the phenomenon of dose fade, since the treatment duration was longer for the alternating regimen.

In comparisons of the results obtained for final and cumulative dose intensities, it should be noted that the values are not precisely identical due to the slightly different mathematical calculations used and to the weighting differences described above.

To see whether any associations existed with an assortment of other variables, chi-square tests were performed, primarily to test whether any inherent bias present would produce unwanted relationships. No statistically significant association of dose intensity with any of the variables was found using the 30-day cumulative-dose-intensity method, which is taken to indicate low-level inherent bias at most. For the FDI method, a significantly higher percentage of blacks, of subjects with bone metastases, and of patients showing moderate or less WBC toxicity were found in the high dose-intensity group (Table 3). Altogether, there were three P values of <0.05. No conclusions are justified, since 2 or 3 such cases might be expected by chance alone out of 52 comparisons. If a 'trend' is defined as corresponding to a P value of between 0.05 and 0.15, then five trends were identified. As determined by both methods of dividing subjects into dose-intensity groups, trends were observed only for tumor response, which was associated with high dose intensity in both cases. This conforms with Skipper's conclusions relating to dose-intensity studies in animals [25]. In the FDI analysis, the trend for time to progression supported a correlation of short time to progression with high dose intensity, and this was considered to be a spurious trend.

The purpose of this communication was to present, demonstrate, and discuss methods for the calculation of received dose intensity and to make the reader aware that the methods used to discriminate high from low dose intensity may vary. Of particular importance is the observation that definitions of high or low received dose intensity can be contrived to ensure correlations with outcome. Therefore, standard methods of reporting dose intensity should be adopted to avoid a deluge of dose-intensity data in the literature that are not comparable. Ideally, the standard methods should be those that show the most meaningful predictive or correlative value. For the MAOP 2183 data, no such relationship is obvious. This agrees with the findings of the meta-analysis of Klasa et al. [17] for small-cell lung cancer, whereby no consistent influence of dose intensity on outcome could be shown. Different results may be obtained for treatment of other types of primary neoplasms, in which dose intensity is likely to play a more important role, or in situations in which more variability occurs in the dose intensity obtained for the treated population.

References

1. Anderson JR, Santarelli MT, Peterson B (1990) Dose intensity in the treatment of diffuse large-cell lymphoma. J Clin Oncol 8: 1927
2. Baar J, Tannock I (1989) Analyzing the same data in two ways: a demonstration model to illustrate the reporting and misreporting of clinical trials. J Clin Oncol 7: 969
3. Carter WH Jr, Wampler GL, Stablein DM (1983) Regression analysis of survival data in cancer chemotherapy, vol 44. Marcel Dekker, New York, p 131
4. Cohen MH (1990) What determines actual chemotherapy dose intensity? J Clin Oncol 8: 1926
5. Coppin CML (1987) The description of chemotherapy delivery: options and pitfalls. Semin Oncol 14 [Suppl 4]: 34
6. Crawford SM, Newlands ES, Begent RHJ, Rustin GJS, Bagshawe KD (1989) The effect of intensity of administered treatment on the outcome of germ cell tumours treated with POMB/ACE chemotherapy. Br J Cancer 59: 243
7. DeVita VT Jr, Hubbard SM, Young RC, Longo DL (1988) The role of chemotherapy in diffuse aggressive lymphomas. Semin Hematol 25 [Suppl 2]: 2
8. Dodwell DJ, Gurney H, Thatcher N (1990) Dose intensity in cancer chemotherapy. Br J Cancer 61: 789
9. DuBois D, DuBois EF (1916) A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 17: 863
10. Fukuoka M, Furuse K, Saijo N, Nishiwaki Y, Ikegami H, Tamura T, Shimoyami M, Suemasu K (1991) Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. J Natl Cancer Inst 83: 855
11. Henderson IC, Hayes DF, Gelman R (1988) Dose-response in the treatment of breast cancer: a critical review. J Clin Oncol 6: 1501
12. Horning SJ, Kwak LW, Halpern J, Olshen RA (1990) Reply (to reference 1). J Clin Oncol 8: 1927
13. Hryniuk WM (1988) The importance of dose intensity in outcome of chemotherapy. In: DeVita VT Jr, Hellman S, Rosenberg SA (eds) Important advances in oncology. J.B. Lippincott, Philadelphia, p 121
14. Hryniuk W, Bush H (1984) The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 2: 1281
15. Hryniuk WM, Goodyear M (1990) The calculation of received dose intensity. J Clin Oncol 8: 1935
16. Hryniuk WM, Figueredo A, Goodyear M (1987) Application of dose intensity to problems in chemotherapy of breast and colorectal cancer. Semin Oncol 14 [Suppl 4]: 3
17. Klasa RJ, Murray N, Coldman AJ (1991) Dose-intensity metaanalysis of chemotherapy regimens in small-cell carcinoma of the lung. J Clin Oncol 9: 499
18. Kwak LW, Halpern J, Olshen RA, Horning SJ (1990) Prognostic significance of actual dose intensity in diffuse large-cell lymphoma: results of a tree-structured survival analysis. J Clin Oncol 8: 963
19. Levin L, Hryniuk W (1987) The application of dose intensity to problems of ovarian and endometrial cancer. Semin Oncol 14 [Suppl 4]: 12
20. Miles DW, Earl HM, Souhami RL, Harper PG, Rudd R, Ash CM, James L, Trask CWL, Tobias JS, Spiro SG (1991) Intensive weekly chemotherapy for good-prognosis patients with small-cell lung cancer. J Clin Oncol 9: 280
21. Miller TP, Dahlberg S, Weick JK, Files JC, Eyre HJ, Pendergrass KB, Fisher RI (1990) Unfavorable histologies of non-Hodgkin's lymphoma treated with ProMACE-CytaBOM: a groupwide Southwest Oncology Group study. J Clin Oncol 8: 1951
22. Nichols CR, Tricot G, Williams SD, Besien K van, Loehrer PJ, Roth BJ, Akard L, Hoffman R, Goulet R, Wolff SN, Giannone L, Greer J,

Einhorn LH, Jansen J (1989) Dose-intensive chemotherapy in refractory germ cell cancer – a phase I/II trial of high-dose carboplatin and etoposide with autologous bone marrow transplantation. J Clin Oncol 7: 932

23. Nichols CR, Williams SD, Loehrer PJ, Greco FA, Crawford ED, Weetlaufer J, Miller ME, Bartolucci A, Schacter L, Einhorn LH (1991) Randomized study of cisplatin dose intensity in poor-risk germ cell tumors: a Southeastern Cancer Study Group and Southwest Oncology Group protocol. J Clin Oncol 9: 1163
24. Roth BJ, Johnson DH, Greco FA, Einhorn LH, Goodlow JL, Cherng N, Randolph JA, Schacter LP (1989) A phase III trial of etoposide (E) and cisplatin (P) versus cyclophosphamide (C), doxorubicin (A), and vincristine (V) versus alternation of the two therapies for patients (PTS) with extensive small cell lung cancer (SCLC): preliminary results. Proc Am Soc Clin Oncol 8: 225
25. Skipper HE (1990) Dose intensity versus total dose of chemotherapy: an experimental basis. In: DeVita VT Jr, Hellman S, Rosenberg SA (eds) Important advances in oncology. J.B. Lippincott, Philadelphia, p 43
26. Tannock IF, Boyd NF, DeBoer G, Erlichman C, Fine S, Larocque G, Mayers C, Perrault D, Sutherland H (1988) A randomized trial of two dose levels of cyclophosphamide, methotrexate and fluorouracil chemotherapy for patients with metastatic breast cancer. J Clin Oncol 6: 1377
27. Wampler GL, Heim W, Ellison NM, Ahlgren JD, Fryer JG (1991) Comparison of cyclophosphamide, doxorubicin, and vincristine with an alternating regimen of methotrexate, etoposide, and cisplatin/cyclophosphamide, doxorubicin, and vincristine in the treatment of extensive-disease small-cell lung carcinoma: a Mid-Atlantic Oncology Program study. J Clin Oncol 9: 1438