Eur J Cancer Clin Oncol, Vol. 18, No. 8, pp. 747–754, 1982.
Printed in Great Britain.

0277-5379/82/080747-08$03.00/0

Duration of Complete Response to Chemotherapy in Advanced Breast Cancer

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Abstract—*Twenty-seven patients with advanced breast cancer with complete response (CR) to chemotherapy have been analysed and observed for up to* 8 years. *Median time to attainment of CR was* 8.1 months (*range*, 1–19.5) *and median duration of CR was* 27.5 months (1–97 + months). *Most* (16) *recurrences occurred in the first* 2 years. *In* 12 *patients* (63%) *relapse was at sites initially involved. No clear relationship between the duration of CR and a variety of prognostic factors or the dose of cytotoxic drugs given was found, although there was a tendency to longer duration of CR when fewer sites were involved. The presence of visceral disease did not preclude a prolonged CR. It seems that despite some patients surviving many years, relapse is inevitable and cure of the disease is unlikely with presently available chemotherapy.*

INTRODUCTION

ADVANCED breast cancer is sensitive to cytotoxic chemotherapy, but few patients have a complete response. The duration of complete response is variable and can range from a few weeks to many years. This report relates the duration of complete response to a number of prognostic factors including the clinical course of the disease before chemotherapy, previous treatment and sites of disease. An analysis has also been carried out to study the effect of the dose of cytotoxic drugs administered.

MATERIALS AND METHODS

Patients

Six hundred and forty-seven consecutive patients treated by cytotoxic chemotherapy for advanced breast cancer were studied. Two hundred and seventy-five of these patients had been treated in 3 prospective randomised clinical trials which have been reported previously [1–3]; 99 had either had cyclophosphamide (C) alone or in combination with 5-fluorouracil (F), methotrexate (M) and vinblastine (Vb) [1], and 176 had been treated with adriamycin (A) +/− vincristine (Vc) before crossing over to a combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) [2, 3] (some of these 176 had received concomitant norethisterone acetate). The remaining 372 patients had been treated empirically with a variety of regimens.

All patients had progressive disease before chemotherapy was started. Full clinical examination was undertaken during which all palpable lesions were measured, in two perpendicular axes when possible, and colour photographs taken of visible lesions. A skeletal survey was carried out which for patients treated early in the study was radiological, but in latter years was by an isotropic bone scan with radiographs of areas of increased uptake. Baseline chest radiographs, and haematological and biochemical screens were done and liver scans performed when indicated clinically or biochemically. Physical examination was repeated every 3–4 weeks, depending upon the chemotherapy schedule, with repeat measurements and photographs. Radiographs for assessment were repeated 3-monthly.

Response was assessed by the UICC criteria [4]. Complete response (CR) was defined as the disappearance of all known disease determined by 2 observations not less than 4 weeks apart. In the case of bone metastases all lesions must have been shown radiologically to have calcified. The duration of complete response was measured from the date complete response was first recorded to the date on which progressive disease was noted. Survival is recorded from the date of starting chemotherapy to the date of death.

All complete responders in this study have been observed for at least 2 years, with a maximum follow-up of 8 years. The date of last follow-up for the purpose of this study was 31 July 1981.

Oestrogen receptor content of tumours was available for patients in the latter part of the

Accepted 10 March 1982.
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period of this study and was estimated by the method of King *et al.*[5]. Tumours having a concentration of less than 5 fmol/mg cytosol protein were considered to be negative (ER-).

Differences between groups of variables were analysed using either the Chi-square test or Student's *t* test. Duration of response and survival were analysed using the log rank method [6].

The chemotherapy regimens and methods for the calculation of doses administered are described in the Appendix.

RESULTS

Out of the whole series of 647 patients only 27 were documented as having achieved CR on chemotherapy. However, of the 372 patients who were treated empirically, because of ineligibility for the 3 prospective trials, many had had treatment started shortly before death. In the 275 patients treated within the clinical trials, 18 (6.5%) achieved CR. All 27 complete responders have been considered in the following analysis. The characteristics of these patients with regard to age, menopausal status, stage at presentation and oestrogen receptor status are shown in Table 1, previous treatment is outlined in Table 2 and sites of metastatic disease are shown in Table 3. The distribution of the chemotherapy regimens is shown in Table 4.

In general, chemotherapy was given according to the protocols, but this was not always possible. Due to progression of disease, AVc had to be changed to CMF after 3 courses in one patient, CR occurring during CMF. In 4 other patients CMF had to be substituted after 2, 3, 4 and 7 courses of A +/− Vc due to suspected cardiotoxicity. In a further patient chemotherapy was changed to CMF after 6 courses of AVc because of neurotoxicity.

The median time from starting chemotherapy to achievement of CR was 8.1 months

Table 1. Characteristics of the complete responders

Mean age at diagnosis (years)	50 (range, 27–68)
Mean age at beginning of chemotherapy (years)	54 (range, 30–69)
Menopausal status at diagnosis (No. patients)	
Premenopausal	13 (48%)
Postmenopausal	14 (52%)
Clinical stage at representation (No. patients)	
I	5
II	10
III	8
IV	2
Unknown	2
Estrogen receptor status (No. patients)	
Positive	7
Negative	5
Unknown	15

Table 2. Previous treatment of the complete responders

	No. patients
Primary treatment	
Simple or radical mastectomy +/− local radiotherapy	15
Radiotherapy alone	6
Wide excision and local radiotherapy	2
Radiotherapy and oophorectomy	1
Oophorectomy	1
Fluoxymesterone	1
Chemotherapy	1
Endocrine treatment for advanced disease	
Estrogens, androgens, progestogens, prednisone or tamoxifen	15
Ovarian ablation	11
Hypophysectomy	7
Adrenalectomy	1

Table 3. Distribution of disease in the complete responders

	No. patients	%
Sites of metastases		
Breast	8	30
Contralateral breast	7	26
Skin	19	70
Lymph nodes	18	67
Skeletal	7	26
Lung	5	19
Pleural	5	19
Liver	2	7
Mediastinum	1	4
Peritoneum	1	4
Number of sites involved		
1	3	11
2	10	37
⩾3	14	52
(median, 2.7 sites; range, 1–5)		
Dominant site involved		
Visceral	13	48
Bone	4	15
Soft tissue	10	37

Table 4. Regimens of chemotherapy received by complete responders

Regimen	No. patients
Adriamycin +/− vincristine followed by CMF	16
Adriamycin +/− vincristine followed by CMF with concomitant norethisterone acetate	7
Cyclophosphamide alone	3
CMF + vinblastine	1
Total	27

(range, 1–19.5 months). The median time to CR was more rapid in the absence of skeletal metastases (6.6 months vs 11.4 months).

The median duration of CR was 27.5 months (range, 1–97+ months). Nineteen of the 27 patients (70%) relapsed at times ranging from 1 to 51 months after attainment of CR. Twelve patients (63%) relapsed at sites initially involved at the start of treatment, while in 7, relapse occurred at previously uninvolved sites, 2 of these being in the brain. Eight patients (30%) continue in CR for from 31 to 97+ months after the attainment of CR. In the 3 patients who discontinued treatment while still in CR, 2 continue in CR at 56+ and 97+ months, having stopped treatment at 46 and 28 months respectively; the patient who stopped treatment at 12 months at her own request relapsed at 39 months. The probability of response duration in relation to the number of sites involved is shown in Fig. 1. This shows a tendency to longer duration of CR in patients with less than 2 sites involved, but the difference is not statistically significant ($\chi^2 = 1.746$). The longest duration of CR with subsequent recurrence occurred in a patient relapsing in the brain after 51 months. The only other patient to relapse in the brain did so just one month after attainment of CR. Figure 2 shows the distribution of patients in relation to duration of CR.

The presence of visceral disease did not preclude a prolonged CR to chemotherapy. One patient who had extensive liver metastases, confirmed at laparotomy, is the longest responder, at 97+ months. A further patient had suffered cardiac tamponade due to a malignant pericardial effusion and continues in CR on chemotherapy at 47+ months.

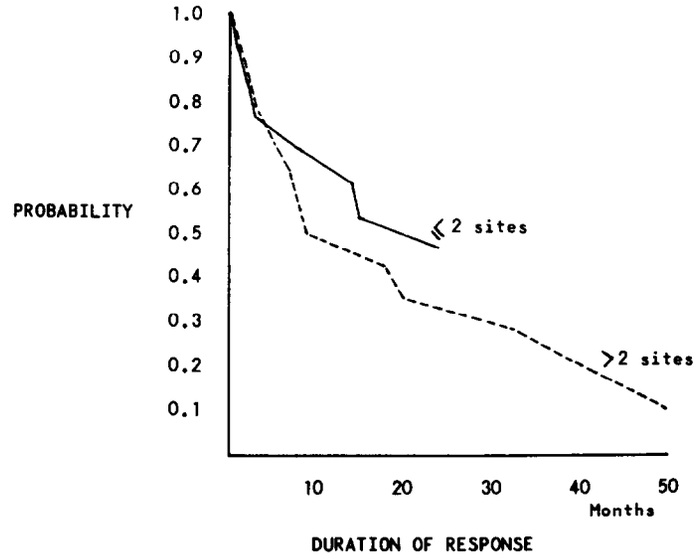


Fig. 1. Probability of response duration in relation to the number of sites involved with metastatic disease.

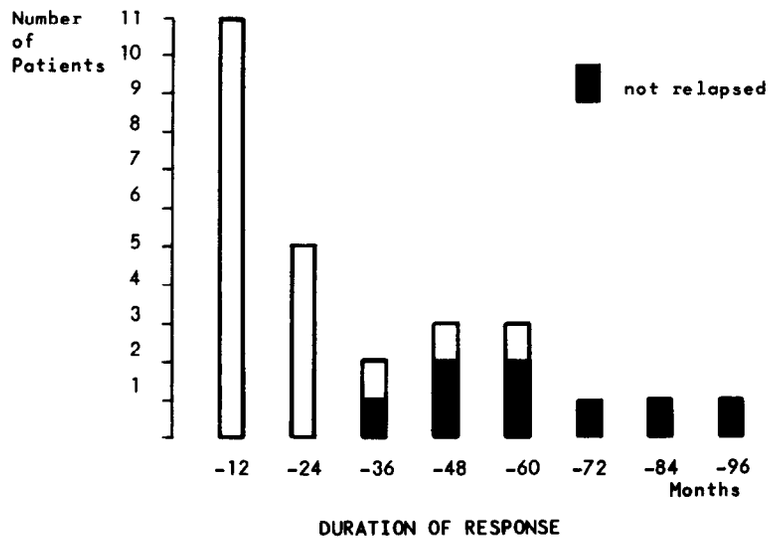


Fig. 2. Distribution of patients in relation to duration of complete response.

Most of the recurrences (16 patients) have occurred in the first 2 years after the attainment of CR, only 3 patients having relapsed after this time. Arbitrarily, the patients have been divided into short-term responders (CR less than 30 months) or long-term responders (CR greater than or equal to 30 months). The characteristics between these two groups are compared in Table 5, which shows that no statistically significant difference occurred between the groups for any variable except for the size of the primary tumour at first diagnosis ($P < 0.05$).

The combined mean relative doses of drugs given over successive time periods is shown in Fig. 3. There is a trend for the doses to decrease with time. For example, the combined mean relative dose of A→CMF was 88%, decreasing to 70% after 144 weeks. The number of patients starting each time period decreases as patients relapse. The mean relative doses for continuous cyclophosphamide are seen to be considerably lower than for the combinations, probably attributable to the continuous nature of this regimen leading to a greater myelotoxicity than with an intermittent regimen.

The probability of response duration in

*Table 5. Comparison of characteristics of short and long-term complete responders**

	Duration of complete response		
	<30 months ($n = 16$)	⩾30 months ($n = 11$)	Significance†
Mean age at diagnosis	51.4 yr	47.6 yr	N.S.
Mean age at beginning of chemotherapy	55.5 yr	51.9 yr	N.S.
Mean age at menarche	13.8 yr	12.9 yr	N.S.
Mean age at menopause	48.1 yr	47.1 yr	N.S.
Mean age at first full pregnancy	27.4 yr	29.9 yr	N.S.
Duration of symptoms before diagnosis	4.7 months	4.0 months	N.S.
Disease-free interval after primary treatment	29.1 months	21.5 months	N.S.
Time from diagnosis to chemotherapy	47.7 months	52.1 months	N.S.
Time from start of chemotherapy to complete remission	6.8 months	7.9 months	N.S.
Maximum diameter of primary tumour at diagnosis	6.8 cm	4.0 cm	$t = 2.12$; $P < 0.05$
Menopausal status at diagnosis			
Premenopausal	6	7	N.S.
Postmenopausal	10	4	
Family history of breast cancer			
Yes	6	5	N.S.
No	10	6	
Parity			
⩽2 children	12	9	N.S.
>2 children	4	2	
Clinical stage at diagnosis			
I	4	1	
II	4	6	
III	5	3	N.S.
IV	1	1	
Unknown	2	0	
Axillary node status at diagnosis			
Involved	10	9	
Not involved	4	2	N.S.
Unknown	2	0	
Estrogen receptor status			
Positive	5	2	
Negative	4	1	N.S.
Unknown	7	8	
Primary treatment			
Mastectomy +/−			
Radiotherapy	8	7	N.S.
Radiotherapy alone	3	3	N.S.

*Numbers refer to numbers of patients unless otherwise stated.
†N.S. = not significant.

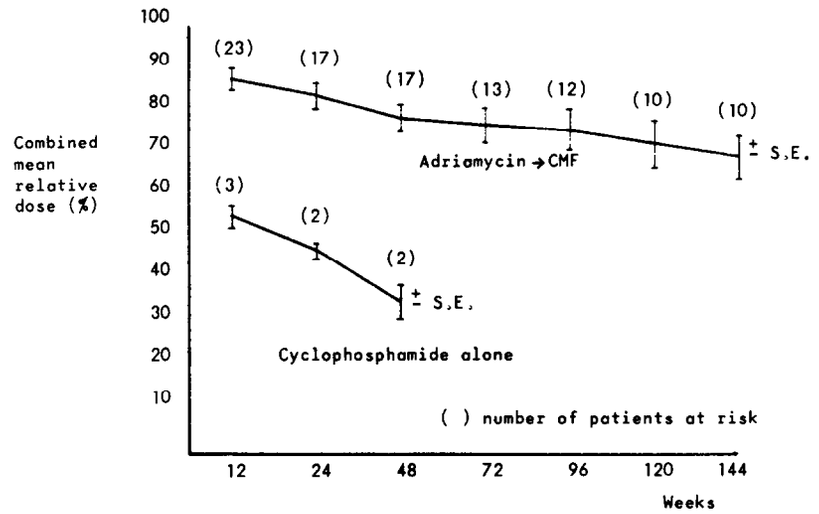


Fig. 3. To illustrate the reduction in combined mean relative doses of drugs over consecutive time periods.

relation to the combined mean relative doses of A→CMF after 12 weeks of chemotherapy is shown in Fig. 4, in which patients receiving equal to or greater than 80% of the combined mean relative dose is compared to those receiving less than 80%. There is no statistically significant difference between these response duration curves ($\chi^2 = 0.138$). Similarly, analyses comparing other dose percentages for a variety of time periods showed no significant differences.

The survival curve for all 27 complete responders in this series is shown in Fig. 5. This shows an exponential fall without any tendency to flatten, indicating that even very long-term responders are unlikely to be cured of the disease. All 9 patients with CR longer than 36 months are still alive, whereas 16/18 patients with CR < 36 months have died.

DISCUSSION

The attainment of complete response in advanced breast cancer must be a pre-requisite for there to be any chance of eradicating all disease by systemic treatment. In this series the achievement of complete response was uncommon, occurring in only 6.5% of 275 patients treated on prospective controlled trials. This frequency of complete response is somewhat lower than that reported in 2 other series specifically studying complete responders (11 and 19% respectively) [7, 8]. However, the median duration of response in this series of 27.5 months (range 1–97+ months) was longer than in other reports, and this may reflect the prolonged continuation of treatment in this series rather than those in which treatment was stopped after 2 years [8]. The presence of visceral disease does not preclude a complete and

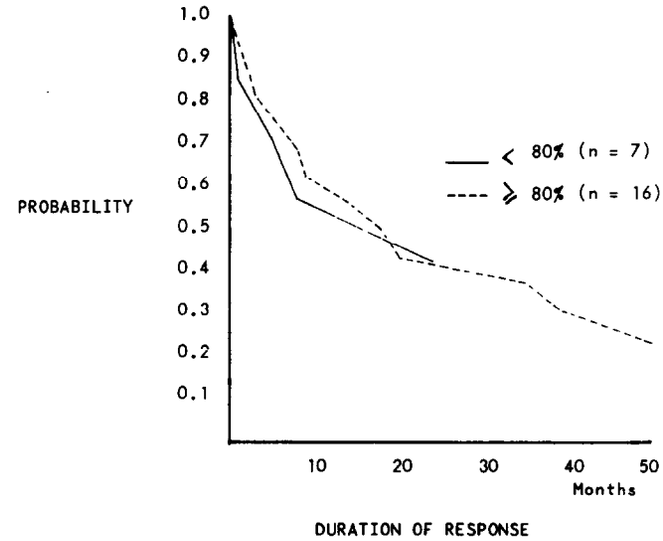


Fig. 4. Probability of complete response in relation to the combined mean relative dose of A→CMF after 12 weeks of chemotherapy.

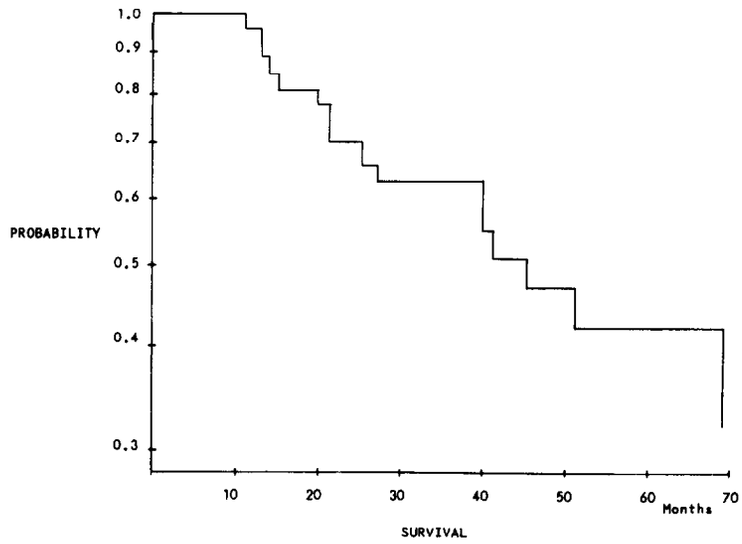
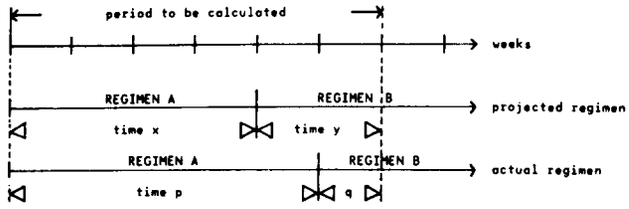


Fig. 5. Probability of survival for all 27 complete responders.



REGIMEN A: DRUGS A_i $A_1, A_2, .., A_i, ... A_n$ A_i for i = 1,n

REGIMEN B: DRUGS B_j $B_1, B_2, ..., B_j, ... B_m$ B_j for j = 1,m

Projected dose for drugs of Regimen A for time x = e

Projected dose for drugs of Regimen B for time y = f

Actual dose for drugs of Regimen A in time p = a

Actual dose for drugs of Regimen B in time q = b

(note p > x in view of hypothetical delays in treatment)

	REGIMEN A	REGIMEN B
projected dose per week	$\frac{e_{A_i}}{x}$ for i = 1,n	$\frac{f_{B_j}}{y}$ for j = 1,m
actual dose per week	$\frac{a_{A_i}}{p}$ for i = 1,n	$\frac{b_{B_j}}{q}$ for j = 1,m
relative dose per week (%)	$\frac{a_{A_i/p}}{e_{A_{i/x}}} .100$ for i = 1,n	$\frac{b_{B_{j/q}}}{f_{B_{j/y}}} .100$ for j = 1,m
	$\frac{100x}{p} . \left(\frac{a_{A_i}}{e_{A_i}}\right)$ for i = 1,n	$\frac{100y}{q} . \left(\frac{b_{B_j}}{f_{B_j}}\right)$ for j = 1,m
mean relative dose per week (%)	$\frac{100x}{p} . \frac{\sum_{i=1}^{n} \left(\frac{a_{A_i}}{e_{A_i}}\right)}{n}$	$\frac{100y}{q} . \frac{\sum_{j=1}^{m} \left(\frac{b_{B_j}}{f_{B_j}}\right)}{m}$
mean relative dose in time p and q (%)	$\frac{\sum_{i=1}^{n} \left(\frac{a_{A_i}}{e_{A_i}}\right)}{n} .100x$	$\frac{\sum_{j=1}^{m} \left(\frac{b_{B_j}}{f_{B_j}}\right)}{m} .100y$
combined mean relative dose of Regimens A+B in time p+q (%)	$\left(\frac{\sum_{i=1}^{n} \left(\frac{a_{A_i}}{e_{A_i}}\right)}{n} .x + \frac{\sum_{j=1}^{m} \left(\frac{b_{B_j}}{f_{B_j}}\right)}{m} .y\right)\left(\frac{100}{p+q}\right)$	

but since x+y = p+q, this reduces to

$$\left(\frac{\sum_{i=1}^{n} \left(\frac{a_{A_i}}{e_{A_i}}\right)}{n} .x + \frac{\sum_{j=1}^{m} \left(\frac{b_{B_j}}{f_{B_j}}\right)}{m} .y\right)\left(\frac{100}{x+y}\right)$$

which it is seen is independent of p and q

Fig. 6. Method for calculation of the combined mean relative dose.

durable response to chemotherapy; the individual patient with the longest duration of complete response (97+ months) had extensive liver metastases.

In agreement with other studies, many patients achieving CR relapsed within 2 years and there is a trend for relapse to occur at sites involved at the start of chemotherapy. The relapse rate in the brain (2/27, 7%) was lower than the 14 and 24% notes in other series [7, 8], but in all instances this is higher than the general incidence of cerebral involvement in breast cancer [9].

These results show that at present, cytotoxic chemotherapy for advanced breast cancer cannot eradicate the disease, even in complete responders. Complete response can last for many years, but relapse seems to be inevitable. There is a tendency for longer response to be associated with a small tumour burden, as judged by the number of sites involved, but no other variables were found to correlate convincingly with duration of complete response. Furthermore, we were unable to demonstrate any dose–response relationship for chemotherapy.

Acknowledgement—We are grateful to Miss Kathy O'Reilly for assistance in the collection of data.

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APPENDIX

Calculation of doses of cytotoxic drugs

Projected dose. The projected dose of the drug is the exact dose that could have been given in a defined period of time according to protocol without any dose modifications at any time. The following regimens were used throughout the period of this study:

1. Adriamycin (A) +/− vincristine (Vc)→ cyclophosphamide (C) + methotrexate (M) + 5-fluorouracil (F) [2, 3]. (a) Patients less than 60 years old: A 70 mg/m^2 i.v. (maximum 120 mg) on day 1; Vc 1.4 mg/m^2 i.v. (maximum 2 mg), days 1 and 8. No drugs, on days 9–21, cycle repeated on day 22. (b) Patients 60 years old or more: A 60 mg/m^2 i.v. (maximum 100 mg) on day 1; Vc 1.4 mg/m^2 i.v. (maximum 2 mg), days 1 and 8. No drugs, days 9–21, cycle repeated on day 22. After 8 cycles of A +/− Vc or on progression of disease or on the development of unacceptable side-effects (including suspected cardiotoxicity), treatment was continued with CMF as follows: (a) Patients less than 60 years old: C 100 mg/m^2 p.o. (maximum 150 mg) on days 1–14; M 30 mg/m^2 i.v. (maximum 50 mg), days 1 and 8; F 600 mg/m^2 i.v. (maxi-

mum 1G), days 1 and 8. No drugs, days 15–28, cycle repeated on day 29. (b) Patients 60 years old or more: C 100 mg/m^2 p.o. (maximum 150 mg) on days 1–14; M 20 mg/m^2 i.v. (maximum 40 mg), days 1 and 8; F 400 mg/m^2 i.v. (maximum 1G), days 1 and 8. No drugs, days 15–28, cycle repeated on day 29.

In the above regimens full doses were given, provided the white blood cell count was greater than 4000/μl and the platelet count greater than 120,000/μl. For a white blood cell count between 2000 and 4000/μl or a platelet count of between 70,000 and 120,000/μl, 50% doses were given. For any counts below the lower limits, treatment was postponed until recovery of bone marrow function was sufficient to allow either 50 or 100% doses.

Treatment was continued indefinitely until the development of progressive disease, except in 2 patients while still in complete remission for the following reasons: (a) complete remission persisting after 46 months of chemotherapy, and in view of previous disease being solely cutaneous it was deemed reasonable to stop treatment; (b) patient's request after 12 months of chemotherapy.

2. Cyclophosphamide alone [1]. Cyclophosphamide was given orally continually in a daily dose according to body weight (body weight less than 48 kg, 200 mg; 48–58 kg, 250 mg; greater than 58 kg, 300 mg). The white blood cell count was checked weekly and treatment was stopped if this fell below 2000/μl; it was re-started when it recovered to 3000/μl. Treatment was continued until disease progression occurred, except in one complete responder who developed protracted leucopenia after 28 months of treatment.

3. Combined cyclophosphamide (C), 5-fluorouracil (F), methotrexate (M) and vinblastine (Vb) [1]. Cyclophosphamide 100 mg daily orally, days 1–15, methotrexate 25 mg i.v., days 1, 8 and 15, 5-fluorouracil 500 mg i.v., days 1, 8 and 15, vinblastine 5 mg i.v., days 1, 8 and 15. No drugs, days 16–42, cycle resumed on day 43. A course was started only if the white blood cell count was above 3000/μl. The second and third injections of methotrexate and 5-fluorouracil (days 8 and 15) were postponed if the white blood cell count fell below 2000, when cyclophosphamide was also stopped. Treatment was continued indefinitely until disease progression.

Actual dose. The actual dose was the dose of cytotoxic drug actually received by a patient in a defined period of time.

Relative dose. The relative dose is the actual dose received in a defined time period divided by the projected dose for the same time period. It is expressed as a percentage. The relative dose for each drug was calculated separately at set periods of time (12, 24, 48, 72, 96, 120 and 144 weeks), always being related to the date of commencement of chemotherapy.

Mean relative dose. In calculating the mean relative dose of the drugs in a given combination over a defined period of time, it was necessary to take certain points into consideration. Drug combinations such as A +/− Vc or CMF were always given sequentially and never simultaneously or in an alternating fashion. Regarding A +/− Vc, as we have found that A alone gives the same response frequency as AVc[3], we have just used the relative dose of adriamycin for this combination. The mean doses of CMFVb was calculated as the mean of all the single relative doses of the drugs in combination.

Combined mean relative dose. When in a defined period of time a cross-over from adriamycin to CMF occurred, the mean relative doses were fractionated according to the duration each combination occupied during the defined time period. The method used to calculate the doses is shown in Fig. 6.