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Original Paper

Dose–Response Effect of Adjuvant Cyclophosphamide, Methotrexate, 5-Fluorouracil (CMF) in Node-positive Breast Cancer

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There is evidence in the literature of a relationship between dose and response to adjuvant chemotherapy for breast cancer, although published results are conflicting. We therefore retrospectively analysed the role of dose response in patients included in four adjuvant trials of the International Breast Cancer Study Group (IBCSG, formerly the Ludwig Breast Cancer Study Group (trials I, II, III and V), all using 'classical' cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). A total of 1385 node-positive patients were treated with oral cyclophosphamide, and intravenous methotrexate plus 5-fluorouracil (CMF) for at least six 4 week courses. 1350 of these were included in 6 month landmark treatment outcome analyses. A total of 1029 patients were premenopausal, 321 were postmenopausal; 800 had one to three and 550 more than three involved axillary nodes at surgery. The median follow-up ranged from 12 years for trial V to 15 years for trials I–III. Patients were grouped according to three prospectively defined dose levels based on the percentage of the protocol prescribed dose that was actually administered (level I $\geq$ 85%, level II 65–84%, level III < 65%). Patients who received dose level II had a higher disease-free ($P = 0.07$) and overall survival ($P = 0.03$) than those who received a higher (level I) or lower (level III) percentage. The 10 year overall survival was 60% for dose level II, 56% for dose level I, 51% for dose level III. The results were generally consistent within trial, menopausal status, and oestrogen receptor status groups. The results within nodal groups showed a large difference among the dose levels for the group with one to three positive nodes ($P = 0.02$), but no difference for the group with four or more positive nodes. Our results indicate that the dose–response effect remains a crucial factor in adjuvant chemotherapy of breast cancer. Reductions larger than 35% in the dose administered of oral CMF adversely influenced the outcome of breast cancer patients and should be avoided. The better outcome of the intermediate dose group indicates the need to investigate other aspects involved in the cytotoxicity of adjuvant CMF chemotherapy. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

THERE IS convincing evidence that adjuvant systemic chemotherapy increases survival of patients with breast cancer. Although large numbers of patients are currently treated with adjuvant chemotherapy and long-term data on relapse-free survival or overall survival (OS) are available, there are conflicting results concerning the role of dose and dose intensity [1–3]. The principle of dose intensity is supported by experimental model systems where a slight increase in the drug dose may result in a large increase in tumour cell kill [4–8]. However, extrapolations from animal tumour systems may be confounding, since the interaction between drugs and human tumours, especially epithelial tumours is very complex [9]. The heterogeneity of epithelial tumours as well as the sophisticated biological mechanisms that protect cells against cytotoxic substances influence clinical results. Bonadonna and colleagues [10, 11] were the first to provide evidence that the favourable outcome of patients treated with adjuvant cyclophosphamide, 5-fluorouracil (5-FU) and methotrexate (CMF) at 5 and 10 years was related to a full-dose treatment. This study generated substantial interest in the dose intensity question; many retrospective analyses confirmed the value of optimal dose intensity as a prognostic feature in patients treated with chemotherapy, while others failed to confirm this hypothesis [12–21]. Obviously, conclusions from these types of retrospective analyses may be biased [22]. Patients capable of receiving full-dose chemotherapy may differ in important characteristics, such as age and performance status, from those who could not tolerate full doses. However, trials refuting the dose–response hypothesis included mostly patients given single-agent or low-dose combination chemotherapy [14, 17, 18].

During the last decade, the Cancer and Leukemia Group B (CALGB) conducted a randomised prospective study evaluating three different doses and dose intensity of adjuvant chemotherapy in node-positive breast cancer [23]. They reported a significantly longer disease-free survival (DFS) and OS for patients treated with a high or moderate dose intensity versus the low dose. Reports of this study renewed interest in the dose question and suggested that doses of chemotherapy should not be reduced if maximal benefit is to be achieved.

Based on these considerations, we retrospectively evaluated the data from four studies of the International Breast Cancer Study Group (IBCSG) evaluating adjuvant CMF in node-positive breast cancer in order to evaluate a possible dose–response relationship.

PATIENTS AND METHODS

Table 1 describes the trials and patients included in this analysis of the IBCSG (formally the Ludwig Breast Cancer Study Group) trials I, II, III, and V. The inclusion characteristics have been described in detail elsewhere [24–27]. Briefly, all patients had histologically confirmed, non-inflammatory, unilateral breast carcinoma staged T_{1-3}, N_{1-2} according to the international TNM classification (tumour-nodes-metastasis). Premenopausal status was defined by normal menstruation, amenorrhoea for less than 1 year, biochemical evidence of ovarian function, amenorrhoea for 1–3 years in patients less than 52 years of age or hysterectomy without bilateral oophorectomy for patients less than 56 years of age. Oestrogen (ER) and progesterone receptors (PgR) ≥ 10 fmoles/mg cytosol protein were considered as positive, and lesser values were considered negative. Additional criteria for patient eligibility, randomisation procedures, chemotherapy dose modifications and follow-up studies have been previously described.

All patients had primary treatment by total mastectomy and axillary clearance. Within 6 weeks they were allocated to receive the treatments detailed in Table 1. Two patients from trial V who were randomised to CMFp×6, but received PeCMF + CMFpT×6, were excluded.

There was no dose reduction prescribed for elderly patients, and the dose of drugs remained constant for each drug cycle. In the presence of myelosuppression, doses were reduced as follows: leucocytes 2500–3900/μl or platelets 75000–99000/μl, doses were reduced by 50%; leucocytes 1000–2499/μl or platelets 50 000—74 900 μl, no drug was delivered and chemotherapy was delayed for 1 week. Blood counts were carried out on days 1 and 8 just before administration of methotrexate and 5-FU. The dose was also reduced by 25% or discontinued in the presence of side-effects other than myelotoxicity, such as stomatitis, gastrointestinal disturbances and chemical cystitis.

Table 1. *Characteristics of IBCSG trials I–III and V*

Trial [Ref.]		Years accrual	Eligible patients	Treatment groups	Median follow-up (years)
I [24]	Premenopausal 1–3 N+	1978–1981	491	CMF×12 cycles versus CMFp×12 cycles every 28 days	15
II [25]	Premenopausal 4+ N+	1978–1981	327	CMFp×12 cycles versus Ox + CMFp×12 cycles	15
III [26]	Postmenopausal age <65 years	1978–1981	463	Observation versus p + T for 1 year versus CMFp + T for 1 year	15
V [27]	Premenopausal	1981–1985	715	PeCMF×1 cycle versus CMFp×6 cycles versus PeCMF (1 cycle) + CMFp×6 cycles	12
V [27]	Postmenopausal	1981–1985	514	PeCMF×1 cycle versus CMFp×6 cycles + T for 6 months versus PeCMF (1 cycle) + CMFp×6 cycles + T for 6 months	12

C, cyclophosphamide (100 mg/m^2 oral days 1–14 of each cycle); M, methotrexate (40 mg/m^2 intravenous days 1 and 8 of each cycle); F, 5-fluorouracil (600 mg/m^2 intravenous days 1 and 8 of each cycle); p, prednisone (7.5 mg/m^2 day oral); T, tamoxifen (20 mg oral once daily); PeCMF, peri-operative CMF; Ox, oophorectomy; N, node.

To categorise patients according to dose level received, three groups were created: level I ($\leq 85\%$ of protocol prescribed full dose); level II (65–84%); level III ($< 65\%$). The mean of the three percentages (actual cyclophosphamide, methotrexate, and 5-FU received of the cyclophosphamide, methotrexate, and 5-FU prescribed) was calculated for each cycle. The average of these means for the first six cycles was used to assign the dose level groups. As shown in Table 2, approximately half the patients overall received at least 85% of the expected dose during the first six cycles. The prescribed dose did not make any provision for dose reductions. The received dose includes the exact amount received, including dose reductions for any reason.

For the purpose of evaluating dose levels in relation to DFS and OS, a 6 month landmark analysis was used [28]. Patients who either had a relapse or were lost to follow-up within the first 6 months were excluded (35 women). Thus, DFS and OS are conditional upon not having an event during the time period in which chemotherapy was given. The total number of patients included in this landmark analysis was 1350 (Table 2). This type of analysis removes the bias that would result from treatment stopping early due to recurrence.

Data available as of January 1997 were used for the analysis. The median follow-up for each trial is shown in Table 1. DFS was defined as the interval from randomisation to relapse, the appearance of a second primary cancer (including a contralateral breast cancer), or death, whichever occurred first. OS was defined as the time from randomisation to death from any cause. Survival curves were estimated using the Kaplan–Meier method [29]. The logrank test was used to test for the significance of differences, and Cox models [30] were used to test for interactions between dose level effects and covariates. All *P* values were two-sided and were stratified by trial when data were pooled across trials.

RESULTS

The patient characteristics among the 1350 patients are presented in Table 2. Because trials in the first generation (I–III) treated all premenopausal patients with CMF, there was a high percentage of premenopausal patients (76%), and the median age was 47 years. ER status was known for 65% of the patients: 61% of these had ER-positive tumours and 39% had ER-negative tumours.

In these trials, the reasons for dose reduction were collected for each cycle of CMF. As shown in Table 3, cycles were most often reduced due to haematological toxicity (2201/3540 cycles) and non-haematological toxicity was responsible for dose reduction in 790 cycles. Overall, 2991/3540 cycles were reduced due to toxicity. Patients were more likely to have a dose reduction as the cycle number

Table 2. Patient characteristics according to study (percentages are in parentheses)

	Trial I	Trial II	Trial III	Trial V	Total
Total eligible cases	485	318	147*	400†	1350
Age Median (years)	45	45	60	51	47
Range	21–59	26–57	50–66	25–70	21–70
Dose level I ($\geq 85\%$)‡	222 (46)	170 (53)	57 (39)	247 (62)	696 (52)
Dose level II (65–84%)	186 (38)	111 (35)	59 (40)	115 (29)	471 (35)
Dose level III ($< 65\%$)	77 (16)	37 (12)	31 (21)	38 (10)	183 (14)
ER negative	118 (24)	89 (28)	19 (13)	121 (30)	347 (26)
ER positive	133 (27)	106 (33)	55 (37)	238 (60)	532 (39)
ER unknown	234 (48)	123 (39)	73 (50)	41 (10)	471 (35)
ER 10–49	98 (20)	76 (24)	17 (12)	105 (26)	296 (22)
ER > 50	35 (7)	30 (9)	38 (26)	133 (33)	236 (17)
Premenopausal	485 (100)	318 (100)	–	226 (57)	1029 (76)
Postmenopausal	–	–	147 (100)	174 (44)	321 (24)
1–3 nodes positive	485 (100)	–	85 (58)	230 (58)	800 (59)
> 3 nodes positive	–	318 (100)	62 (42)	170 (43)	550 (41)

*Includes only CMFp + T for 1 year treatment group. †Includes only CMFp×6 and CMFp×6 + T for 6 months treatment groups. ‡Percentage of protocol prescribed full dose. ER, oestrogen receptor; C, cyclophosphamide; M, methotrexate; F, 5-fluorouracil; T, tamoxifen; p, prednisone.

Table 3. Reasons for dose reduction for each cycle of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) (percentages are in parentheses)

Cycle number	Any dose reduction *n* (%)	Wound healing*	Haematological toxicity	Other toxicity	Other reason	Total cycles
1	278 (21)	2 (0.2)	111 (9)	46 (4)	119 (9)	1299
2	510 (40)	2 (0.2)	325 (25)	96 (8)	87 (7)	1280
3	607 (47)	0	377 (29)	142 (11)	88 (7)	1280
4	672 (53)	1 (0.1)	429 (34)	165 (13)	77 (6)	1266
5	724 (58)	2 (0.2)	481 (39)	169 (14)	72 (6)	1249
6	749 (60)	1 (0.1)	478 (38)	172 (14)	98 (8)	1248
Total	3540 (46)	8 (0.1)	2201 (29)	790 (10)	541 (7)	7622

*Available for trial V only.

increased, from 21% of cycles in cycle one to 60% of cycles in cycle six. This increase was especially marked for reductions due to haematological toxicity. Table 4 summarises the number of cycles actually received according to trial. There were 24 patients who received no CMF. Patient refusal was the most common reason (58%) for never starting CMF. Among all patients, 91% received all or part of six cycles of CMF.

Table 4. *Number of cyclophosphamide, methotrexate and* 5-*fluorouracil (CMF) cycles received within the first* 6 *months (number of patients)*

	0	1	2	3	4	5	6	Total
Trial I	1	8	6	5	4	14	447 (92%)	485
Trial II	5	2	1	3	5	9	293 (92%)	318
Trial III	3	4	3	4	2	6	125 (85%)	147
Trial V	15	1	1	3	3	11	366 (92%)	400
Total	24	15	11	15	14	40	1231 (91%)	1350

Tables 5 and 6 describe the outcome measures (landmark analyses of DFS and OS, 9 respectively) according to the dose levels described earlier. Patients who received level II generally had a higher DFS and OS than those who received a higher (level I) or lower (level III) percentage of their prescribed CMF dose (Tables 5 and 6). The hazard ratios for DFS were: level I versus levels II + III = 0.86 (0.70–1.06); level II versus levels I + III = 0.78 (0.63–0.97). Among the 1350 patients, the 10 year DFS was 48% for dose level II, 42% for dose level I, and 40% for dose level III (Figure 1a, $P = 0.07$). The 10 year OS was 60% for dose level II, 56% for dose level I and 51% for dose level III. The difference was statistically significant for OS (Figure 1b, $P = 0.03$). These results were generally consistent within trial, menopausal group (Figure 2a, b) and ER status group although differences were non-significant. The results within nodal groups showed a large difference ($P = 0.02$) among the dose levels for the lower node group (Figure 3a), but no difference for the higher node group (Figure 3b). Tests for an interaction effect between dose level and nodal group were non-significant ($P = 0.17$ for DFS, $P = 0.07$ for OS).

Table 5. *Disease-free survival (DFS) according to dose level of cyclophosphamide, methotrexate and* 5-*fluorouracil (CMF) (*6 *month landmark analysis)*

		5 year DFS ± SEM			10 year DFS ± SEM			
	No. of patients	I	II	III	I	II	III	*P* value
Trial I	485	69 ± 3	72 ± 3	66 ± 5	57 ± 3	60 ± 4	55 ± 6	0.72
Trial II	318	46 ± 4	49 ± 5	43 ± 8	29 ± 4	31 ± 4	24 ± 7	0.49
Trial III	147	59 ± 7	63 ± 6	55 ± 9	44 ± 7	45 ± 5	26 ± 8	0.19
Trial V	400	53 ± 3	61 ± 5	47 ± 8	38 ± 3	45 ± 5	38 ± 8	0.44
Pre	1029	58 ± 2	63 ± 3	58 ± 4	42 ± 2	49 ± 3	45 ± 4	0.36
Post	321	55 ± 4	63 ± 5	49 ± 7	42 ± 4	44 ± 5	29 ± 6	0.13
1–3N+	800	68 ± 2	73 ± 3	60 ± 5	54 ± 3	60 ± 3	46 ± 5	0.02
>3N+	550	43 ± 3	46 ± 4	48 ± 6	28 ± 3	28 ± 3	29 ± 6	0.90
ER–	347	52 ± 4	61 ± 4	56 ± 9	42 ± 4	51 ± 4	41 ± 9	0.35
ER+	532	58 ± 4	61 ± 4	50 ± 6	39 ± 3	42 ± 4	38 ± 6	0.32
Total	1350	57 ± 2	63 ± 2	56 ± 4	42 ± 2	48 ± 2	40 ± 4	0.07

Dose level I, ≥ 85% of prescribed full dose; dose level II, 65–84% of prescribed full dose; dose level III, < 65% of prescribed full dose. SEM, standard error of the mean; ER, oestrogen receptor; N, node.

Table 6. *Overall survival (OS) according to dose level of cyclophosphamide, methotrexate and* 5-*fluorouracil (CMF) (*6 *month landmark analysis)*

		5 year OS ± SEM			10 year OS ± SEM			
	No. of patients	I	II	III	I	II	III	*P* value
Trial I	485	84 ± 2	87 ± 3	82 ± 4	68 ± 3	72 ± 3	66 ± 5	0.50
Trial II	318	65 ± 4	68 ± 4	57 ± 8	41 ± 4	46 ± 5	34 ± 8	0.38
Trial III	147	70 ± 6	80 ± 5	65 ± 9	58 ± 8	55 ± 7	39 ± 9	0.24
Trial V	400	75 ± 3	76 ± 4	65 ± 8	56 ± 3	57 ± 5	46 ± 8	0.23
Pre	1029	75 ± 2	78 ± 2	74 ± 4	56 ± 2	62 ± 3	55 ± 4	0.16
Post	321	75 ± 4	79 ± 4	62 ± 7	58 ± 4	56 ± 5	41 ± 7	0.07
1–3N+	800	84 ± 2	87 ± 2	74 ± 4	68 ± 2	72 ± 3	56 ± 5	0.004
>3N+	550	64 ± 3	64 ± 3	63 ± 6	41 ± 3	41 ± 4	41 ± 6	0.94
ER–	347	67 ± 3	69 ± 4	63 ± 9	49 ± 4	60 ± 4	46 ± 9	0.31
ER+	532	80 ± 2	83 ± 3	71 ± 6	58 ± 3	57 ± 4	50 ± 6	0.26
Total	1350	75 ± 2	79 ± 2	70 ± 3	56 ± 2	60 ± 2	51 ± 4	0.03

Dose level I, ≥ 85% of prescribed full dose; dose level II, 65–84% of prescribed full dose; dose level III, < 65% of prescribed full dose. SEM, standard error of the mean; ER, oestrogen receptor; N, node.

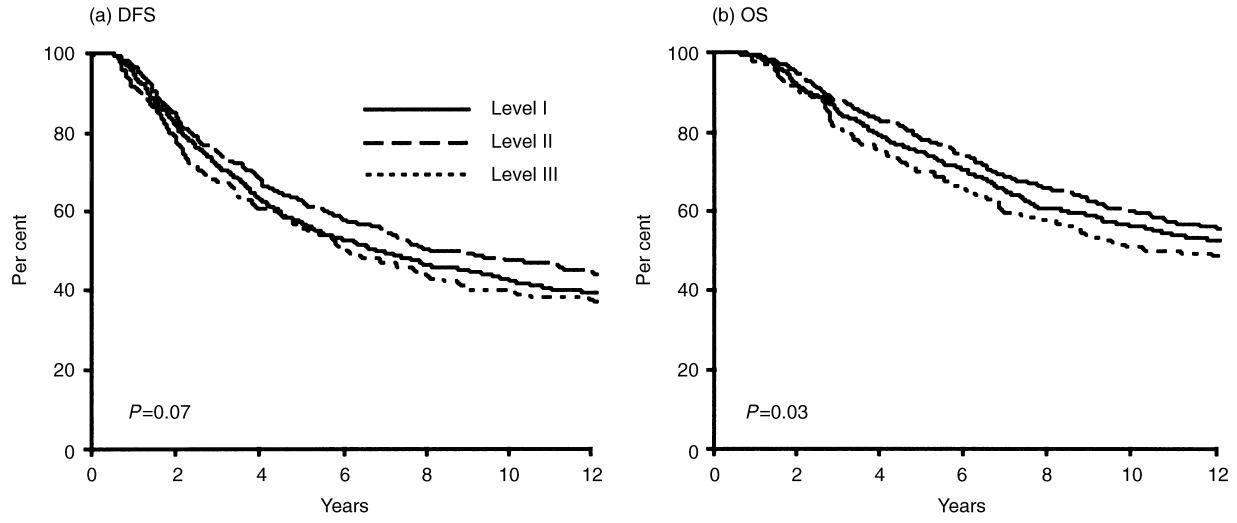

Figure 1. Kaplan–Meier plots for 6 month landmark analyses of (a) disease-free (DFS) and (b) overall survival (OS) according to three dose levels: level I: ≥ 85% of the prescribed dose; level II: 65–84% of the prescribed dose; level III < 65% of the prescribed dose. Median follow-up time was 14 years.

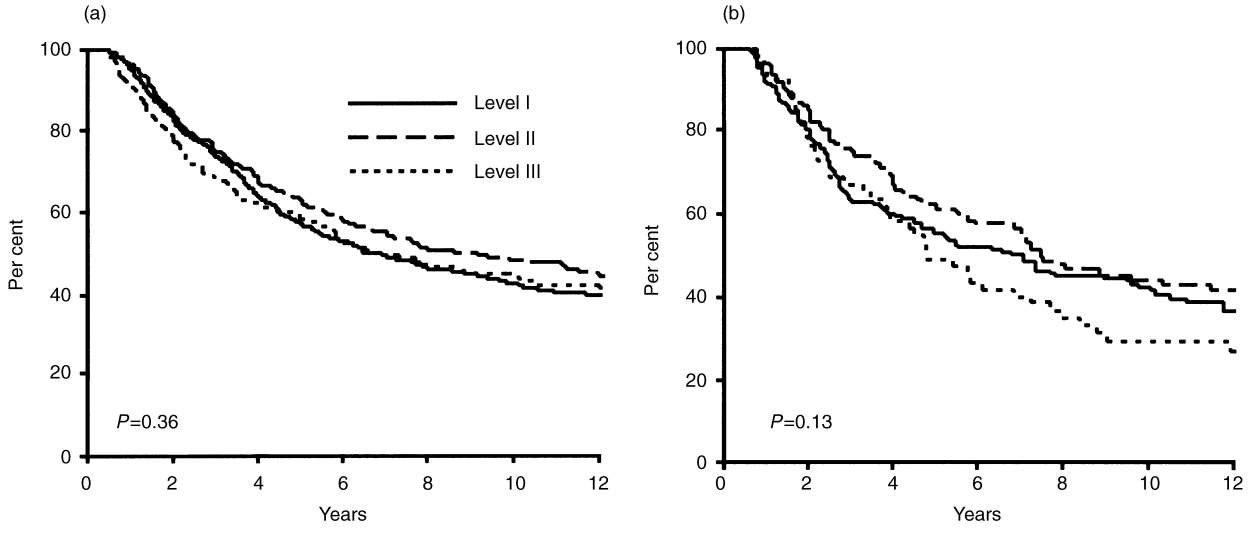

Figure 2. Kaplan–Meier plot for 6 month landmark analyses of disease-free survival according to dose level in (a) 1053 premenopausal patients and (b) 332 postmenopausal patients.

DISCUSSION

The first report that analysed dose response of breast cancer to chemotherapy was from the Milan Cancer Institute [10]. They retrospectively divided into three groups patients included in the first two Milan trials according to cumulative dose of CMF received: ≥ 85%, 65–84%, and < 65%. Patients who received the highest dose of chemotherapy had a significantly longer DFS than patients who received < 65% of the optimal dose with survival differences in favour of patients who had a higher drug dose. The report stimulated similar retrospective analyses, although the dose groups frequently differed from those used in the Milan trial. Only two trials demonstrated an OS advantage for patients who received higher doses of chemotherapy [13, 17]. Some investigators demonstrated only a DFS advantage [10, 13, 14, 16], whereas other groups reported no dose–response effect or even a negative dose effect [12, 19, 22].

In a second type of retrospective analysis based on the dose rate of published data, Hrynjuk and associates [31, 32] demonstrated a strong and positive correlation between dose intensity and outcome. Conversely, Gelman and Henderson [33] performed an analysis on those trials that included CMF with or without vincristine and prednisone, and demonstrated a negative correlation, among premenopausal women although not statistically significant.

To improve the comparison of the results with literature data, the present study used the same dose level groupings originally reported by the Milan group. For the entire patient group, patients who received level II had a higher DFS and OS than those who received a higher (level I) or lower (level III) drug dose. The results were generally consistent within trial, menopausal group and ER status group. The first major conclusion from the analysis was that patients who received < 65% of the planned dose had a clearly worse outcome than

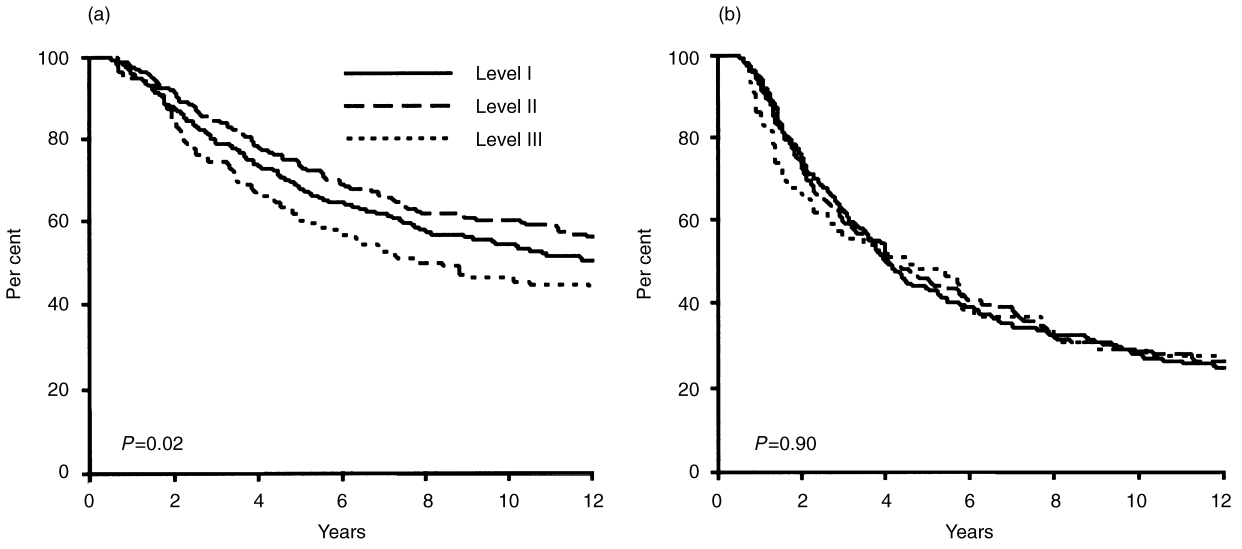

Figure 3. Kaplan–Meier plot for 6 month landmark analyses of disease-free survival according to dose level in (a) 815 patients with one to three positive nodes and (b) 570 patients with more than three positive nodes.

the other groups. These results are consistent with those reported by Bonadonna and Valagussa [10], where a worse outcome was observed for patients included in this dose level than patients who received more than 85% of the prescribed dose. The second point is that patients who received the highest dose had a worse outcome than the intermediate dose group. Although unexpected, there are several explanations for these findings.

As reported in Table 3, dose reductions were mostly attributable to side-effects. The expression of side-effects, and in particular myelotoxicity, may be attributable to different pharmacokinetic peaks of the drug that may correlate with a more efficient antitumour effect. Therefore, the fact that patients receiving a moderate dose reduction (level II) have the best outcome may be attributable to a better absorption and, thus, efficacy of the drugs. It may be postulated that for adjuvant chemotherapy the clinically achieved effect, as evidenced by moderate toxicity, better correlates with survival than the total dose delivered.

The fact that the lower dose group (level III) had the worst outcome, may be explained by a threshold–response effect. The CALGB recently reported the data from a study that randomised patients with node-positive, stage II breast cancer to three different dose and dose intensity levels of doxorubicin, 5-FU and cyclophosphamide. After a median follow-up of 3.4 years, the women treated with a high or moderate dose intensity had significantly longer OS than those treated with a low dose intensity [23]. Such results are consistent with a dose threshold, a dose below which there is no consistent effect, rather than an effect which increases proportionally with increasing doses. In the CALGB trial, the high dose intensity schedule was the most effective regimen in the poor prognostic group of patients who overexpressed the c-*erbB*-2 oncogene. In contrast, no dose response was seen in 71% of patients with no or low c-erbB-2 levels [34]. Such data indicate that the effect of an increased dose in breast cancer may be modulated by different biological baseline features. In fact, the role of c-*erbB*-2 in patients treated with adjuvant CMF was analysed by investigators from the IBCSG group, and a significant correlation between no overexpression and better outcome of the patients was found [35].

Another major issue in the present analysis is that most of the patients analysed were premenopausal (76%) and in this subset of patients the induction of amenorrhoea by CMF has been shown to influence survival. In a previous analysis of trial I by the Ludwig group, a better outcome was observed for patients achieving amenorrhoea after adjuvant chemotherapy [24]. In the present study, the advantage for the intermediate dose was observed particularly in premenopausal patients, whereas in postmenopausal patients there was a similar outcome for levels I and II, thus suggesting a possible influence of the antitumour effect of ovarian function suppression on the results achieved. As previously reported by investigators from the Ludwig group, there was no evidence of a relationship between the dose received and the induction of amenorrhoea, thus suggesting that this antitumour activity may be distributed among all three dose levels.

It is noteworthy that the results within nodal groups showed a marked difference among the dose levels for the lower node group (Figure 3a), but no difference among the higher node group (Figure 3b). Such data are consistent with previously reported data from Bonadonna and Valagussa [10], where a significant difference in outcome was observed only for patients with less than four positive nodes, indicating that for patients with four or more positive nodes, factors other than dose response of CMF influence outcome.

A major drawback in this type of analysis is the difficulty assessing whether the difference in recurrence rate is related to the difference in dose delivered or in the difficulty for the patients to tolerate chemotherapy for factors also associated with a greater likelihood of recurrence, such as bone marrow invasion [22]. The results of the present study, where the highest dose did not correlate with better survival, suggest that other factors are involved.

A further major problem relates to the possible influence of concomitant hormonal treatments, such as prednisone, oophorectomy and tamoxifen, on the treatment results. In fact, low-dose prednisone was administered in the majority of

patients included in the analysis (Table 1). However, Ludwig trial I failed to demonstrate a difference between patients treated with CMF plus prednisone and patients that received CMF alone in terms of DFS and OS [24]. Similar results were reported in Ludwig trial II with the combination of oophorectomy and CMFp versus CMFp alone [25]. Finally, tamoxifen was administered only in postmenopausal patients included in trials III and V [26, 27]. As shown in Figure 2a, the difference between the three dose levels in terms of DFS (level II > level I > level III) was observed in both premenopausal and postmenopausal patients, and was consistent within each of the trials analysed.

The recently reported results from a Canadian study demonstrate the advantage of an anthracycline-containing regimen over 'classical' CMF (with cyclophosphamide given orally in both regimens), in terms of both DFS and OS in premenopausal women with axillary node-positive breast cancer [36]. However, the latter combination still has an important role as an adjuvant treatment of breast cancer. In fact, combined CMF and tamoxifen was recently shown to be more effective than endocrine therapy alone in receptor-positive, node-negative patients, irrespective of menopausal status [37]. Our results indicate that the dose–response effect remains a crucial factor in adjuvant chemotherapy of breast cancer. Reduction in the dose administered of oral CMF by > 35% of the planned dose adversely influences the outcome of breast cancer patients and should be avoided. The better outcome of the intermediate dose group implies that other aspects, such as biological features, should be investigated further.

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