Annals of Oncology 7: 245–250, 1996.
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Original article

The effect of adjuvant prednisone combined with CMF on patterns of relapse and occurrence of second malignancies in patients with breast cancer

G. Marini, S. Murray, A. Goldhirsch, R. D. Gelber, M. Castiglione-Gertsch, K. N. Price, M. H. N. Tattersall, C.-M. Rudenstam, J. Collins, J. Lindtner, F. Cavalli, H. Cortés-Funes, A. Gudgeon, J. F. Forbes, E. Galligioni, A. S. Coates & H.-J. Senn

For the International (Ludwig) Breast Cancer Study Group

Summary

Background: The addition of low-dose prednisone (p) to the adjuvant regimen of cyclophosphamide, methotrexate, 5-fluorouracil (CMF) allowed patients to receive a larger dose of cytotoxics when compared with those on CMF alone. However, disease-free survival and overall survival were similar for the two groups. To test the hypothesis that low-dose prednisone might influence the efficacy of the cytotoxic regimen used, the toxicity profiles of the two treatment regimens and the patterns of treatment failure (relapse, second malignancy, or death) were examined.

Patients and methods: 491 premenopausal and perimenopausal patients with one to three positive axillary lymph nodes included in International (Ludwig) Breast Cancer Study Group (IBCSG) trial I from 1978 to 1981 and randomized to receive CMF or CMFp were analyzed for differences in long-term outcome and toxic events. The 250 patients assigned to CMF and prednisone received on the average 12% more cytotoxic drugs than those who received CMF alone.

Results: The 13-year DFS for the CMFp group was 49% as compared to 52% for CMF alone, and the respective OS percents were 59% and 65%. Several toxic effects such as leukopenia, alopecia, mucositis and induced amenorrhea were reported at a similar incidence in the two treatment groups. Using cumulative incidence methodology for competing risks, we detected a statistically significant increase in first relapse in the skeleton for the CMFp group at 13 years follow-up with a relative risk (RR) of 2.06 [95% confidence interval (CI), 1.23 to 3.46; $P = 0.004$]. Patients with larger tumors in the CMFp regimen were especially subject to this increase with a RR for failure in the skeleton of 3.32 (95% CI, 1.57 to 7.02; $P = 0.0005$). CMFp-treated patients also had a larger proportion of second malignancies (not breast cancer), with RR of 3.34 (95% CI, 0.91 to 12.31; $P = 0.09$).

Conclusions: Low-dose continuous prednisone added to adjuvant CMF chemotherapy enabled the use of higher doses of cytotoxics. This increased dose had no beneficial effect on treatment outcome, but was associated with an increased risk for bone relapses and a small, not statistically significant increased incidence of second malignancies. The effects of steroids, which are widely used as antiemetics (oral or pulse injection) together with cytotoxics, should be investigated to identify their influence upon treatment outcome.

Key words: adjuvant therapy, breast cancer, CMF, patterns of relapse, prednisone, secondary neoplasm

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Introduction

The cyclophosphamide, methotrexate, 5-fluorouracil (CMF) regimen has been widely evaluated. Since the first report of its success in the adjuvant setting [1] for reducing relapses and mortality, the regimen has been modified in a variety of ways without sufficient study of the influence that these modifications might have on treatment outcome. The CMF combination chemotherapy was based on Cooper's 1969 communication, reporting the effectiveness of the regimen in advanced breast cancer [2]. This CMF regimen was composed of cyclophosphamide (C) given orally for 14 consecutive days (100 mg/sqm body surface), with methotrexate (M), 40 mg/sqm i.v. followed by 5-fluorouracil (F) 600 mg/sqm i.v., both on days 1 and 8 of a 28-day course. The Cooper regimen used C given daily, continuously, and weekly M and F. It also contained weekly vincristine (V) and daily prednisone (P). There have been attempts to assess the effectiveness of various combinations of C, M, and F, with and without vincristine and prednisone in advanced disease, but the reported results by Dr. Cooper have never been replicated [3]. A trial in advanced disease suggested that the CMF with C given orally every four weeks, as described above, provided more effective disease control in terms of time to progression and survival when compared with the same regimen given intravenously once every three weeks [4]. In addition, reducing the dose of CMF was shown to be associated with a worse outcome [5].

In the adjuvant setting, the use of prednisone was investigated in a Cancer and Acute Leukemia Group B (CALGB) trial of 712 patients who received either CMFVP or CMF. The results were only partially reported [6]; premenopausal women with 1–3 N+ disease had a better disease-free survival and overall survival if

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they received CMFVP. The Eastern Cooperative Oncology Group (ECOG) trial of 371 premenopausal women [7, 8] showed no statistical difference in outcome in the group which received CMF with prednisone with or without tamoxifen, as compared with CMF alone. In this trial prednisone was given in a dose of 40 mg/sqm daily for 14 days together with cyclophosphamide.

The International (Ludwig) Breast Cancer Study Group (IBCSG) conducted a trial (trial I) in 491 premenopausal and perimenopausal women with 1–3 involved axillary nodes in whom CMF was compared with CMF plus low-dose, daily prednisone (CMFp) [9]. There were two reasons for adding low-dose prednisone to the chemotherapy: (1) the empirical perception that prednisone improved subjective tolerance, and (2) the results of a Canadian trial in which premenopausal women who underwent adjuvant oophorectomy had a better treatment outcome with the concomitant use of prednisone as compared to ovarian ablation alone [10]. In the first report of the Ludwig study, no significant differences in overall survival or disease-free survival were detected between the two groups at 4 years' median follow-up [9]. The study did demonstrate that higher doses of CMF could be delivered to patients who also received low-dose prednisone as compared to those who received CMF alone.

Experiments conducted almost three decades ago indicated that steroids may block the enzyme activation of cyclophosphamide by inhibiting the microsomal enzyme metabolism of the drug [11, 12]. In the current evaluation of the trial we wished to determine whether there were distinct patterns of metastatic presentation in patients who received prednisone compared with those who did not. Since the early Ludwig trials were conducted during a period when steroids were not usually given as antiemetics, a common use of steroids today, this trial provides an unconfounded comparison of CMFp *versus* CMF.

Patients and methods

Data from 491 patients with node-positive breast cancer who entered the IBCSG (formerly Ludwig) trial I from 1978 to 1981 were analyzed. All patients had at least a total mastectomy and axillary clearance as the primary treatment. Patients did not receive adjuvant radiotherapy.

These pre- and perimenopausal patients with 1 to 3 involved axillary lymph nodes were randomly allocated to receive either 12 cycles of CMF (cyclophosphamide, methotrexate and 5-fluorouracil) or CMFp (CMF with the addition of continuous, low-dose prednisone) to evaluate the impact of low-dose prednisone added to combination chemotherapy. The CMF regimen was composed of cyclophosphamide (C) given orally for 14 consecutive days, 100 mg/sqm per day; and methotrexate (M), 40 mg/sqm i.v. followed by 5-fluorouracil (F), 600 mg/sqm i.v.; both on days 1 and 8 of a 28-day course. A continuous administration low-dose prednisone was given at a dose of 7.5 mg/day (5 mg A.M. and 2.5 mg P.M.). Follow-up policy was standardized: clinical, hematological and biochemical assessment was required every three months for two years, and thereafter every six months until death. Chest X-rays were required every six months; bone scans were required every six months for two years and then annually. All patient data, including all disease and survival related events, were reviewed and classified by the medical study coordinator (A.G.).

Disease-free survival was defined as the interval from randomization to relapse, the appearance of a second primary cancer (including a contralateral breast cancer), or death, whichever occurred first. Evidence for breast cancer events was recorded as acceptable in the presence of a positive cytological or histological finding, or of tumor progression demonstrated through prospectively defined imaging tests. Bone metastases were backdated to when first suspected. Overall survival was defined as time from randomization to death from any cause. Survival curves were estimated by the Kaplan–Meier method [13] and standard errors were calculated using Greenwood's formula [14]. The log-rank test was used to test for the significance of differences between disease-free and overall survival curves for CMF *versus* CMFp [15]. Gray–Tsiatis linear rank tests were used in addition to the log-rank test in order to test for later hazard differences [16]. Cumulative incidence functions [17] were estimated for each of the competing sites of first failure, and tests of differences between treatment groups were conducted [18]. All *P*-values were two-sided. Sites of first relapse were classified according to their impact on prognosis [19]: (1) local, regional, and distant soft tissue or nodal metastases; (2) bone alone or with local, regional, or soft tissue or nodal metastases; (3) viscera alone or with either bone or local, regional or soft-tissue or nodal metastases. Contralateral breast cancer, second non-breast cancer malignancies, and deaths without malignancies were also recorded as separate categories. Any event was considered to be a component of the first event if diagnosed within a two-month time frame [19].

Results

The results of this trial were previously reported in 1985 at 4 years' median follow-up [9]. At that time no significant differences were detected with respect to disease-free or overall survival. At 13 years' median follow-up, we are focusing on long term disease-free and overall survival, and sites of first relapse. Figure 1 displays the Kaplan–Meier plots for disease-free and overall survival. A non-significant separation in the disease-free and overall survival probabilities favoring CMF alone developed after five years' median of follow-up. Table 1 presents the treatment comparisons for all patients and the major subgroups of patients including estrogen receptor status, tumor size, and age. The 13-year disease-free survival (DFS) percentage for the

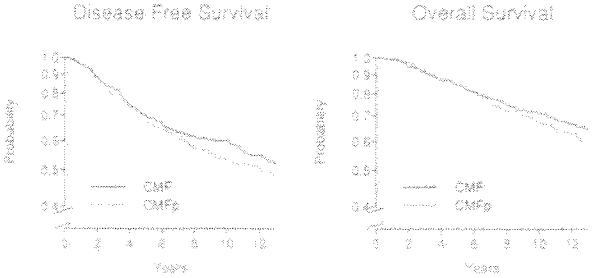

Figure 1. Disease-free survival and overall survival according to treatment assignment for IBCSG (Ludwig) Trial I. The CMF treatment group is indicated by a solid line, and the CMFp group is indicated by a dotted line. The median follow-up is 13 years.

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Table 1. IBCSG trial I: DFS and OS by treatment within patient subpopulations (13 years' median follow-up).

	Patients	Failures (deaths)	13-Year DFS percent (%) + s.e.	*P*-value	13-Year OS percent (%) + s.e.	*P*-value
All patients						
CMF	241	114 (83)	52 ± 3	0.39	65 ± 3	0.30
CMFp	250	127 (98)	49 ± 3		59 ± 3	
ER-positive[a]						
CMF	64	31 (23)	51 ± 7	0.72	65 ± 6	0.50
CMFp	71	38 (30)	43 ± 7		59 ± 7	
ER-negative						
CMF	59	23 (16)	62 ± 6	0.62	73 ± 6	0.29
CMFp	60	25 (22)	56 ± 7		63 ± 6	
ER unknown[a]						
CMF	118	60 (44)	47 ± 5	0.61	61 ± 5	0.88
CMFp	119	64 (46)	47 ± 5		61 ± 4	
Tumor size ≤ 2 cm						
CMF	118	57 (40)	52 ± 5	0.92	65 ± 5	0.92
CMFp	117	55 (41)	52 ± 5		66 ± 5	
Tumor size > 2 cm						
CMF	123	57 (43)	52 ± 5	0.25	65 ± 4	0.21
CMFp	133	72 (57)	45 ± 5		53 ± 5	
Age < 40						
CMF	55	32 (25)	41 ± 7	0.61	51 ± 7	0.77
CMFp	61	38 (25)	37 ± 7		55 ± 7	
Age ≥ 40						
CMF	186	82 (58)	55 ± 4	0.52	68 ± 4	0.17
CMFp	189	89 (73)	52 ± 4		60 ± 4	

[a] ER-positive = ≥10 fmol/mg protein, 52% of the patients had estrogen receptors assessed in the trial which recruited patients between 1978 and 1981.

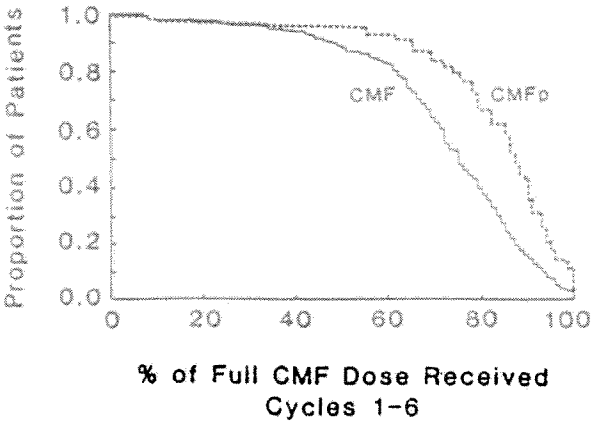

Figure 2. Proportion of patients who received at least the indicated average total dose of CMF for each of the two treatment arms. The CMF arm is indicated by a solid line, and the CMFp arm is indicated by a dotted line. The areas under the curves represent the average amount of CMF received. This figure was reproduced with permission from Cancer Res 1985; 45: 4454–9.

Table 2. Incidence of toxicities of any grade and severe or worse according to treatment group.

	CMF		CMFp		*P*-value any grade
	Any grade	Severe or worse[b]	Any grade	Severe or worse[b]	
Leukopenia	90%	1%	82%	2%	0.03
Nausea/vomiting	77%	14%	80%	13%	0.77
Stomatitis/mucositis	23%	4%	31%	3%	0.12
Diarrhea	20%	0%	20%	1%	0.63
Alopecia	64%	N/A[a]	72%	N/A[a]	0.04
Induced amenorrhea	84%	N/A[a]	87%	N/A[a]	0.40

[a] N/A, not applicable: severe alopecia and induced amenorrhea were not defined.
[b] Toxicities of grade 3 or grade 4.

CMFp group was 49% compared to 52% for CMF alone [relative risk (RR), 1.12, $P = 0.39$] and the respective overall survival (OS) percentages were 59% and 65% (RR, 1.17, $P = 0.30$). Results were similar for the log-rank test and the Gray–Tsiatis test for later hazard differences. The log-rank *P*-values are displayed in Table 1. A statistically non-significant but observable decrease in overall and disease-free survival was associated with CMFp compared with CMF for patients who were older or had larger tumors. This effect was not observed in younger patients or patients with smaller tumors.

The proportion of patients who received the indicated percent of protocol dose during the first 6 courses of CMF was larger for those who also received low-dose prednisone as clearly indicated in Figure 2. On the average, 72% of full CMF dose in cycles 1 to 6 was received by CMF-treated patients as compared with 83% for the CMFp-treated patients. The incidences of any toxicity and severe or worse toxicity were similar in the two treatment groups, as shown in Table 2. Fewer patients who received CMFp experienced leukopenia (90% for CMF *versus* 82% for CMFp; $P = 0.03$). However, more patients were recorded to have alopecia on the CMFp treatment arm (64% for CMF *versus* 72% for CMFp; $P = 0.04$).

Differences in sites of first relapse, occurrence of another primary neoplasia (not breast cancer), and death without cancer according to treatment group were analyzed (Table 3). Patients who received low-dose prednisone had a higher percentage of first relapse in the bone and a higher incidence of second neoplasia. The incidence of other sites of relapse was similar across treatments.

To further assess this apparent difference between the treatment groups with respect to bone recurrences and occurrences of second primaries, estimates of the cumulative incidence for site of first relapse were calculated for subgroups defined by estrogen receptor status, tumor size, and age. There was a statistically significant increase in first relapse in the bone alone or bone with local, regional, or distant soft tissue/nodal metastases for the CMFp treatment group (RR = 2.06; 95% confidence interval (CI) = 1.23 to 3.46; $P = 0.004$) which remained significant after adjusting for multiple tests with Bonferroni's method [20]. This increased risk of bone relapse was largest among patients with tumor size greater than 2 cm (RR = 3.32; 95% CI = 1.57 to 7.02; $P = 0.0005$). When first relapse in the bone was accompanied by a visceral relapse in the same two

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