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On the Safety of Perioperative Adjuvant Chemotherapy with Cyclophosphamide, Methotrexate and 5-Fluorouracil in Breast Cancer

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Abstract—*Combination cytotoxic chemotherapy (intravenous cyclophosphamide, methotrexate and 5-fluorouracil) was administered within* 36 h *of mastectomy to* 1629 *eligible women with operable breast cancer in a randomized controlled clinical trial. Previously reported unpredictable and severe toxic effects were probably due to an interaction between methotrexate and nitrous oxide used in anesthesia. The addition of intravenous 5-formyl-tetrahydrofolate (Leucovorin) and intensification of postoperative monitoring of patients have decreased toxic effects and enhanced the safety of the chemotherapy regimen.*

INTRODUCTION

ADJUVANT treatment has proven to reduce the relapse rate and to prolong survival in patients with early breast cancer [1]. From November 1981 to December 1985 the Ludwig Breast Cancer Study Group accrued patients into a trial designed to investigate whether results might be improved by early commencement of chemotherapy post-mastectomy (Ludwig Trial V). The details of the study design and related methodological issues have been described elsewhere [2, 3]. The one cycle of perioperative combination chemotherapy, initiated within 36 h of mastectomy, consisted of cyclophosphamide 400 mg/m^2, methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2, administered intravenously (i.v. CMF) on days 1 and 8. Unpredictable and severe toxic effects were observed during the first year of accrual, and have been described [4]. In November 1982 the following changes were made to the treatment protocol in an effort to reduce these toxic effects:

1. Leucovorin 15 mg i.v. was given 24 h after the first i.v. CMF and orally 24 h after the day 8 administration because of the assumption that methotrexate might interact with nitrous oxide on tetrahydrofolate metabolism.
2. Intravenous hydration for 36 h after mastectomy was required.
3. More stringent dose modification criteria were applied to day 8 i.v. CMF:
   (a) no drugs to be given if any stomatitis was observed, and
   (b) no methotrexate to be given if day 8 serum creatinine was $\geq$106 μmol/l.
4. WBC, platelets and serum creatinine determinations were required on day 15, and
5. Patients older than 65 years were excluded from entry into the trial.

This report describes the toxic effects of the perioperative adjuvant chemotherapy before and after these modifications.

MATERIALS AND METHODS

As of December 1986, 2466 evaluable patients were included in the analysis; 1629 of them received perioperative chemotherapy and 837 did not. During the first year of study accrual 468 patients received i.v. CMF without Leucovorin. Investigators were urged to monitor the patients very carefully during the postoperative phase. Side-effects and complications of surgery were prospectively collected and graded on a specific form. A report of noteworthy toxic events was distributed monthly by the Coordinating Center.

Statistical comparisons were done using chi-square tests.

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RESULTS

(a) *Postoperative mortality and life-threatening toxicity*

As described previously, four patients died postoperatively following treatment with CMF alone [4], one of pneumonia with severe myelosuppression on day 15, one of respiratory, hepatic and renal failure on day 40, one of septic shock with myelosuppression on day 15, and the fourth of pulmonary embolism due to deep venous thrombosis on day 7. During the remaining 3 years of study accrual 1161 patients received Leucovorin 24 h after CMF administration as part of the perioperative chemotherapy regimen. One patient who received the i.v. CMF therapy with Leucovorin, and another who received no adjuvant chemotherapy died on day 16 post-mastectomy due to pulmonary embolism. The incidence of postoperative death was significantly lower for the groups receiving i.v. CMF with Leucovorin or no perioperative adjuvant therapy than for the group receiving i.v. CMF alone ($P = 0.02$).

Three other patients, two of whom received Leucovorin, had life-threatening complications from which they fully recovered. The first of these was a 48-year-old women who had septicemia in conjunction with severe myelosuppression on day 14 following days 1 and 8 i.v. CMF without Leucovorin. This patient also had a severe wound edge necrosis after mastectomy which required surgery on day 21. She had been severely burned on the breast at 4 years of age and had received low-dose radiation therapy to the site 10 years ago to decrease keloid formation. The second patient was 45 years old and developed a massive deep venous thrombosis on day 8 after perioperative day 1 CMF and Leucovorin. The third, a 41-year-old patient who had had lung tuberculosis in the past, had sepsis and severe myelosuppression following i.v. CMF and Leucovorin.

(b) *Other toxicities*

A summary of toxic effects reported in the postoperative period is described in Table 1. Patients who received i.v. CMF with Leucovorin experienced lower incidences of stomatitis, renal function impairment, cystitis, alopecia, systemic and local infections, and hematomas, as compared with patients who received i.v. CMF alone. The overall incidence of postoperative complications attributable to the perioperative programs were substantially influenced by the reporting of seromas. A higher incidence of postoperative complications was reported for the groups receiving the chemotherapy regimens.

Table 2 describes the correlation between the incidence of stomatitis, the time from end of mastectomy to initiation of the i.v. CMF therapy, and the use of Leucovorin as part of this treatment regimen. The use of Leucovorin was associated with a smaller percentage of patients treated within the first 6 h ($P = 0.0002$) and also with a lower incidence of stomatitis ($P = 0.001$).

The myelosuppression due to the perioperative chemotherapy is described in Table 3 and in Fig. 1. Significant reductions in severe leukopenia ($<1000/mm^3$) ($P = 0.06$) and thrombocytopenia ($<50{,}000/mm^3$) ($P = 0.001$) were observed with the addition of Leucovorin. However, the overall incidence of leukopenia of any grade ($<4000/mm^3$) was similar.

DISCUSSION

The observed changes in incidence of specific toxic effects raise the following three questions:

(a) *Has there been a significant reduction in toxic effects such as wound healing problems and stomatitis which were hypothesized to be due to an interaction between nitrous oxide and methotrexate?*

Both mild and moderate as well as severe stomatitis were significantly reduced with the addition of i.v. Leucovorin to the perioperative regimen (Table 1). By considering stomatitis in correlation with the time from end of anesthesia (end of mastectomy) it became evident that the main reduction in the incidence of mucosal damage occurred in patients who received treatment within the first 6 h (Table 2). This supports the hypothesis that methotrexate-related toxicity which was enhanced by nitrous oxide could be significantly reduced by i.v. 5-formyltetrahydrofolate (Leucovorin) given 24 h later [5–7].

(b) *Did perioperative chemotherapy increase the incidence of postoperative complications?*

Complications in the postoperative period are usually poorly described in adjuvant trials primarily because patients with severe or persistent morbidity are not entered into these studies. The group with no adjuvant perioperative treatment had a postoperative mortality of 0.1%, similar to that of the group who received i.v. CMF and Leucovorin. The severe local infection rate which was higher for the CMF-without-Leucovorin group decreased to the level seen in patients without perioperative treatment as a consequence of the changes introduced into the trial. The higher incidence of seromas and delayed wound healing which did not require any additional intervention (mild and moderate grades) might be due to the fact that these complications were detected and reported more intensively during the increased monitoring of the patients required by the study protocol. Note that the percentage of patients with midcourse blood counts also increased substantially (Table 3). The incidence of thrombophlebitis and thrombosis was higher in both treatment groups when compared with the group without perioperative treatment. A higher incidence of these side-

Table 1. Postoperative complications and chemotherapy-related toxic effects other than myelosuppression. The impact of the addition of Leucovorin rescue and other protocol alterations

	Percentage of group*					
	Perioperative CT				No perioperative CT	
	Without Leucovorin (n = 468)		With Leucovorin n = 1161		n = 837	
Deaths	0.9%		0.1%		0.1%	
Events reported as toxicity	*mild/mod.*	*severe*	*mild/mod.*	*severe*	*mild/mod.*	*severe*
Nausea and vomiting	65.2%	0.2%	67.0%	1.5%	—	—
Diarrhea	4.1%	0%	6.3%	0%	—	—
Stomatitis	11.5%	1.5%	7.5%	0.4%	—	—
Eye disorders (conjunctivitis)	1.9%	0%	1.5%	0%	—	—
Renal function impairment	0.6%	0.2%	0.3%	0%	—	—
Cystitis	1.9%	0%	0.8%	0.1%	—	—
Liver function impairment	0.2%	0.2%	0.8%	0%	—	—
Depression/neurotoxicity	1.5%	0%	1.7%	0.3%	—	—
Alopecia	9.6%	—	5.5%	—	—	—
Reported as postoperative complication or toxicity						
Systemic infection	1.9%	1.3%	1.6%	0.5%	0%	0.1%
Thrombophlebitis, thrombosis	1.5%	0.4%	1.4%	0.3%	0.1%	0.1%
Wound dehiscence	2.4%	0.9%	2.9%	0.2%	1.3%	0%
Necrosis	1.3%	0.2%	1.0%	0.3%	1.0%	0.2%
Local infection	5.6%	1.3%	3.2%	0.2%	1.9%	0.4%
Seroma	6.2%	0%	11.5%	0.1%	5.9%	0.1%
Hematoma	1.7%	0.2%	0.9%	0.3%	0.7%	0.1%
Local hemorrhage	0%	0.2%	0.3%	0.3%	0.1%	0.2%
At least 1 postoperative complication						
Including seroma	16.2%	3.0%	19.2%	1.6%	9.8%	1.2%
Excluding seroma	11.5%	3.0%	9.6%	1.6%	4.8%	1.2%

*Does not include 37 patients who were eligible for the trial but did not receive assigned treatment. Of these, 31 patients were assigned to perioperative treatment (PeCT) and did not receive it, and five patients were assigned to No-PeCT and received some.

Table 2. Incidence of reported stomatitis in patients who received perioperative adjuvant CMF combination chemotherapy without or with Leucovorin by time from end of mastectomy

Time to first i.v. administration	Percentage of patients with stomatitis (No. of patients) CMF	CMF + Leucovorin
0–6 h	26.7% (45)	1.9% (53)
7–24 h	11.9% (219)	7.2% (414)
≥25 h	11.3% (204)	8.6% (694)
Overall	13.0% (468)	7.8% (1161)

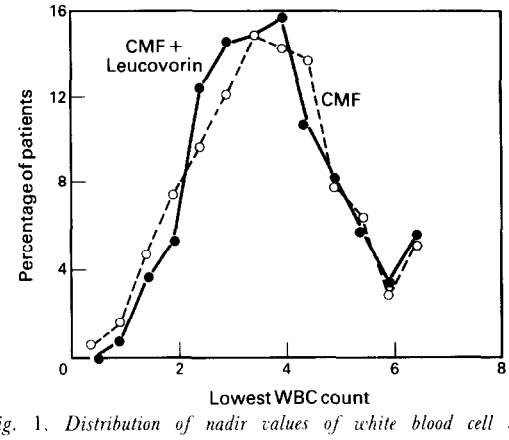

Fig. 1. Distribution of nadir values of white blood cell counts (× 1000/mm³) for 1331 patients who had mid-course counts after administration of perioperative CMF with or without Leucovorin.

effects has been described in series of adjuvant therapy in postmenopausal patients with chemotherapy [8] or with chemo-endocrine therapy [9].

(c) *Did the use of Leucovorin decrease the toxic effects of the i.v. CMF regimen to an extent which could jeopardize tumor cell kill?*

Myelosuppression induced by a chemotherapy regimen is an indication that some degree of cytotoxicity has been achieved. There was a significant reduction of severe leukopenia (<1000/mm³) in the patients who received Leucovorin, while the overall proportion of patients who had some grade of leuko-

Table 3. Chemotherapy-related hematologic toxic effects. Impact of addition of Leucovorin to i.v. CMF perioperative regimen

	Percentage of group (No. of patients)	
	i.v. CMF alone	i.v. CMF + Leucovorin
All patients (No.)	(468)	(1161)
Percentage of patients with mid-course counts	71.8% (336)	85.8% (995)
Nadir WBC/mm^3 for patients with mid-course counts		
3999–2500	40.8%	44.4%
2499–1000	22.0%	21.1%
<1000	2.1%	0.8%
Percentage of patients with mid-course platelet counts	68.4% (320)	84.9% (986)
Nadir platelets/mm^3 for patients with mid-course counts		
99,000–75,000	4.1%	0.7%
74,000–50,000	1.9%	0.4%
<50,000	2.2%	0.2%

penia did not decrease (Fig. 1). Unless a severe grade of leukopenia is required to achieve adequate tumor cell kill, the introduction of Leucovorin is unlikely to have compromised cytotoxic efficiency. Any grade of leukopenia was asssociated with better outcome in a retrospective analysis of Ludwig trials I and II (premenopausal patients with axillary node involvement: Ludwig Breast Cancer Study Group Meeting Minutes, 1986).

In conclusion, the safety of the i.v. CMF regimen was enhanced by the addition of Leucovorin given intravenously 24 h after the first perioperative drug administration and by intensification of the control of patients who received cytotoxic agents in the immediate postoperative period. The question of whether the perioperative use of the combination chemotherapy is clinically relevant must await additional follow-up to study maturation.

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