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Impact of two different dose-intensity chemotherapy regimens on psychological distress in early breast cancer patients

L. Del Mastro[a,*], M. Costantini[b], G. Morasso[c], F. Bonci[d], M. Bergaglio[a], S. Banducci[e], P. Viterbori[b], P. Conte[d], R. Rosso[a], M. Venturini[a]

[a]*Department of Medical Oncology, National Cancer Research Institute, Genova, Italy*
[b]*Unit of Clinical Epidemiology and Trials, National Cancer Research Institute, Genova, Italy*
[c]*Department of Psychology, National Cancer Research Institute, Genova, Italy*
[d]*Department of Medical Oncology, S. Chiara Hospital, Pisa, Italy*
[e]*Unit of Medical Oncology, Hospital of Merate, Italy*

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Abstract

In order to improve outcome, new, often more toxic chemotherapy regimens are continuously investigated in early breast cancer patients. Because the expected survival improvement is small, the possible increase in the negative effects of the new treatments should be carefully evaluated. Negative effects are represented not only by acute and chronic toxicity, but also by the adverse psychological impact of chemotherapy. The aim of this study was to evaluate the effect on patient-reported psychological distress of an increase in the dose-intensity of adjuvant chemotherapy compared with a standard regimen. Psychological distress was evaluated at baseline, during chemotherapy and after 6 and 12 months in breast cancer patients enrolled in a phase III multicentre study comparing the standard adjuvant chemotherapy with cyclophosphamide, epirubicin and 5-fluorouracil every 21 days (CEF21) with the same chemotherapy given every 14 days (CEF14). 392 patients were randomised in participating centres, and 363 were evaluable for this study. Overall, 1095 out of 1446 expected questionnaires (75.7%) were collected and evaluable. At baseline, the mean scores of psychological distress were similar in the two arms. During chemotherapy, a significantly higher psychological distress was observed in the CEF14 compared with the CEF21 arm (32.3 ± 1.3 versus 27.6 ± 1.3; $P = 0.009$), as well as a higher cumulative incidence of anaemia, mucositis, diarrhoea, alopecia, bone pain and fatigue was observed in the CEF14 arm. In multivariate analyses, mucositis ($P = 0.01$), asthenia ($P = 0.059$), and CEF14 treatment ($P = 0.054$) were independently associated with a higher psychological distress. After 6 months, psychological distress was again similar in the two arms and significantly lower when compared with baseline within each arm. A dose-intensive adjuvant regimen induces a higher, although transient, psychological distress in early breast cancer patients. Final results of the randomised trial will indicate whether such higher adverse effects of the dose-intensive regimen are counterbalanced by a higher efficacy of the experimental treatment in terms of survival.

Keywords: Breast cancer; Quality of life; Psychological distress; Adjuvant chemotherapy; Dose-intensity

1. Introduction

Adjuvant treatments are able to improve prognosis of early breast cancer patients [1,2]. At 10 years, adjuvant polychemotherapy induces an absolute survival improvement of approximately 7–11% for women under 50 years and of 2–3% for those aged 50–69 years. Despite this improvement, prognosis, particularly in some subsets, remains poor: the 10-year survival in node-positive patients treated with polychemotherapy is 53 and 49%, for women under 50 years and for those aged 50–69 years, respectively.

These results continue to prompt efforts to improve outcome by the investigation of new chemotherapy regimens, based on the use of different drugs or different strategies, such as an increase in dose or dose-intensity of cytotoxic drugs. Taking into account the benefits in survival observed comparing chemotherapy versus no chemotherapy (ranging from 2 to 11%), the absolute improvement expected with the use of new chemo-

* Corresponding author. Tel.: +39-010-560-0665; fax: +39-010-5600-0850.
E-mail address: ldelmast@hp380.ist.unige.it (L. Del Mastro).

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therapy regimens compared with standard ones is small. Based on such a small, although clinically relevant, expected benefit, the potentially higher adverse effects of new treatments should be taken carefully into account. New chemotherapy regimens are generally more aggressive and toxic compared with standard ones and may have a more negative impact on patients' quality of life by affecting both physical functioning and psychological well-being. It is therefore important to understand whether the potential benefit in terms of survival is worth the negative impact on quality of life.

On the basis of previous trials showing the feasibility and activity of accelerated chemotherapy [3,4], in 1992 the Mammella Inter Gruppo (MIG) group started a randomised phase III multicentre study (MIG-1), comparing a standard adjuvant chemotherapy with cyclophosphamide, epirubicin and 5-fluorouracil, every 21 days (CEF-21), to the same chemotherapy every 14 days (CEF-14) plus granulocyte-colony stimulating factor (G-CSF) in early breast cancer patients. This acceleration (every 14 days) of chemotherapy led to a 50% increase in dose-intensity. The primary end-point of this study was disease-free and overall survival. The secondary end-point was psychological distress evaluated before, during and after chemotherapy. The participation to this secondary evaluation was voluntary, and three centres (Genoa, Pisa and Merate) accepted to participate. The three centres accounted for 35% of the patients randomised in the primary study. The present paper reports the results of this study on psychological distress.

2. Patients and methods

All patients randomised in the MIG-1 trial from November 1992 to November 1996 by the three centres participating in this study were considered eligible for the psychological distress evaluation study. Women with histologically-proven breast cancer who had undergone radical mastectomy or breast-conserving surgery plus full ipsilateral axillary node dissection were eligible for the MIG-1 study if they had involved axillary nodes or were node-negative, but at a high risk of recurrence. In node-negative patients, the high risk was defined as the presence of one or more of the following criteria: age $\leqslant 35$ years, negative oestrogen (ER) and progesterone receptor (PgR) status, tumour size $\geqslant 2$ cm, poor histological grade or high proliferative rate determined by [^{3}H]thymidine labelling index. Other eligibility criteria included no clinical or radiological evidence of distant metastases, adequate bone marrow reserve (white blood cell count $\geqslant 3\times10^9$ cells/l, platelet count $\geqslant 100\times10^9$ cells/l), adequate epatic and renal function and surgery performed not more than 5 weeks before starting chemotherapy. The following were conditions for exclusion: age over 70 years, previous chemotherapy for cancer, pregnancy or lactation, postoperative regional radiotherapy except irradiation limited to the remaining breast after conservative surgery, previous or concomitant malignancy (except curatively treated skin or cervical carcinoma), medical condition precluding anthracycline treatment, drug-requiring psychiatric illness.

After stratification by centre, patients were randomly assigned, by telephone, to receive adjuvant chemotherapy with CEF-21, or the same chemotherapy every 14 days (CEF-14) plus G-CSF. In both arms, chemotherapy was administered intravenously (i.v.) at the same doses (cyclophosphamide 600 mg/m^2, epirubicin 60 mg/m^2 and 5-fluorouracil 600 mg/m^2) for six cycles. CEF-14 patients self-administered subcutaneously (s.c.) G-CSF at a dose of 5 mcg/kg from day 4 to day 11, from cycles one to five. Patients with ER-positive tumours received tamoxifen at 20 mg/day. Postoperative regional radiotherapy limited to the remaining breast was given to patients who had received conservative surgery. The study was approved by the Protocol Review and Ethical Committees of the National Cancer Institute of Geneva, and of each collaborating centre. All patients gave their written informed consent before study entry.

2.1. Design and objectives

The objective of the study was to evaluate the effect on patient-reported psychological distress, of an increased dose-intensity adjuvant chemotherapy as compared with the standard during treatment and in the first year after chemotherapy. Psychological distress assessment was scheduled at baseline (T0), i.e. prior to the start of chemotherapy; during chemotherapy (T1): 42 (range 30–70) days after the first cycle; and at two follow-up visits: 180 (range 150–240) and 365 (range 300–450) days after the first cycle (T2 and T3 assessments).

2.2. Assessment methods

Patients were assessed for toxicity before each cycle of chemotherapy by means of the World Health Organization (WHO) scoring criteria. Psychological distress was assessed by means of the Psychological Distress Inventory (PDI). The PDI is a five-point, 13-item self-assessment scale, developed and validated in Italy as a global measure of psychological distress in cancer patients [5]. It evaluates the general emotional condition of the patient and the psychological disorders related to illness adjustment. The global score, after linear transformation, ranges from 0 to 100 with higher scores reflecting a greater distress. The distribution of the scores among patients in different phases of disease in the validation study may allow PDI changes to be inter-

preted in this clinical trial and their clinical importance. After linear transformation, the lowest psychological distress was in patients with no evidence of disease (PDI mean ± standard deviation (S.D.) = 24.3 ± 14.0) compared with patients undergoing antineoplastic treatment (PDI mean ± S.D. = 37.1 ± 19.1) and to patients under palliative therapy (PDI mean ± S.D. = 44.3 ± 16.1) [5].

3. Statistical methods

3.1. Compliance with psychological distress assessment

Compliance with the assessment schedule and reasons for no assessment were evaluated and compared between the two arms of treatment. Compliance was defined as the number of received forms as a proportion of those expected. Patients died or relapsed were not included in the denominator for the calculation of compliance.

3.2. Missing data

An analysis on missing data was performed to test the hypothesis that reasons for missing assessment were unrelated to the patient's psychological distress (Missing at Random). One check was provided by the comparisons of the PDI scores (means ± standard error of the mean (S.E.M.) between groups of patients with and without psychological distress assessment, at the various scheduled assessments.

3.3. Primary analysis

Data were analysed by comparing the distribution of the scores of all the received questionnaires at each time point using a *t*-test for unpaired data. An analysis of variance for repeated measures was fitted to the data set obtained after single imputation of missing data under the assumption of data Missing at Random. This approach underestimates the S.E.M., but allows inclusion in the analyses the patients with at least two measurements available. In this analysis, PDI baseline scores were introduced in the model as a covariate.

3.4. Toxicity and psychological distress

The relationship between psychological distress and toxicity was analysed among all patients with questionnaires available at baseline and during chemotherapy. The distribution of the main toxicities during chemotherapy was examined as the worst toxicity observed at the time the questionnaire was administered. Differences between the two arms were tested by means of the Chi-square test. The association between toxicity and psychological distress was analysed by comparing the psychological distress during chemotherapy (adjusted means ± S.E.M.) for different levels of toxicities. Adjusted means were obtained using baseline values as a covariate. To test the hypothesis that a higher proportion of distressing toxicity could explain differences in psychological distress during chemotherapy, a multivariate regression model including toxicities and treatment effect was fitted to the data. In this analysis, the dependent variable was the psychological distress during chemotherapy, while baseline psychological distress was introduced in the model as a covariate.

4. Results

392 patients were randomised by the three participating centres (Fig. 1). 29 (7.4%) patients did not fill in any questionnaire and were excluded from the analysis: 3 refused, 1 was illiterate and 14 decided to be followed by another centre; the remaining 11 patients did not fill in any questionnaires due to medical staff errors. Overall, 363 patients were evaluable and their characteristics are reported in Table 1. Demographic and clinical characteristics were comparable in the groups.

4.1. Compliance with the psychological distress assessment

6 patients (3 in each arm) relapsed or died between the first and the second follow-up visits. Of the 1446 expec-

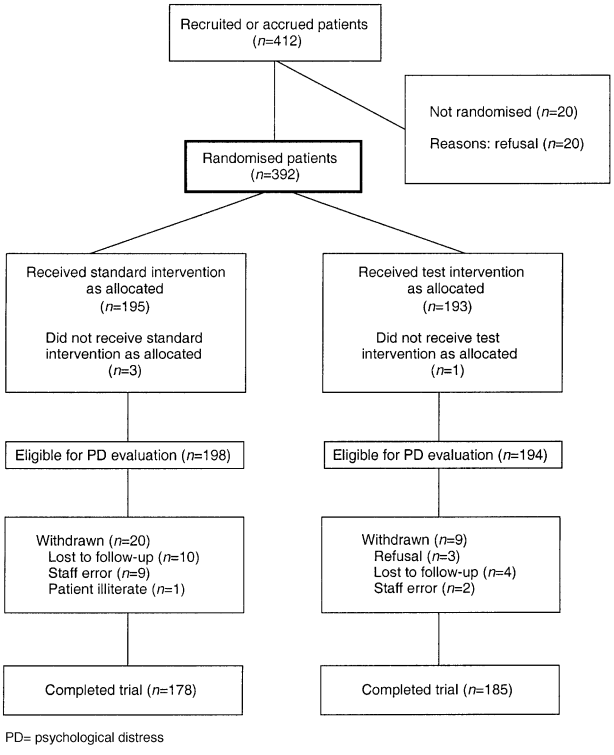

Fig. 1. Flow chart of the progress of patients through the trial (adapted from Ref. [13]).

ted questionnaires, 1095 (75.7%) were collected at the four scheduled assessments, and were evaluable for the analysis (Table 2). Reasons for non-compliance were staff errors ($n=274$), loss of the patient during chemotherapy or follow-up ($n=41$), and patient refusal ($n=36$). The proportion of evaluable questionnaires decreased from 90% at baseline to 83% during chemotherapy, and to 63 and 67% at the two follow-up visits (6th month and 1st year, respectively). A higher proportion of questionnaires was received among patients treated in the experimental arm (CEF-14) at each of the four scheduled assessments. Overall, there was no relationship between form completion and demographic and clinical characteristics reported in Table 1, except for a significantly ($P=0.004$) higher proportion of missing forms during chemotherapy for patients with lower education. The distribution of the mean scores of the PDI according to compliance at the scheduled assessments (Table 3), does not indicate a significant violation of the assumption of Missing at Random.

4.2. Psychological distress by treatment arm (Table 4 and Fig. 2)

At baseline, the mean scores of psychological distress were similar in the two arms. During chemotherapy, a significantly higher psychological distress was observed in the CEF-14 arm compared with the CEF-21 arm ($P=0.009$). After 6 and 12 months, the psychological distress was again similar in the two arms and significantly lower when compared with baseline assessment within each arm.

4.3. Psychological distress and toxicity during chemotherapy

CEF-14-treated patients experienced a statistically significant higher cumulative incidence of anaemia, mucositis, diarrhoea, alopecia, bone pain and fatigue at the PDI assessment during chemotherapy (Table 5). This finding can in part be explained by the fact that, due to the acceleration in the experimental arm, at the T1 assessment, the number of cycles of chemotherapy received by the CEF-14 patients was higher than CEF-21 patients (3.2 ± 0.5 versus 2.2 ± 0.4, respectively), although the mean ($\pm$S.D.) interval between T0 and T1 assessment was similar in the two arms (46.0 ± 7.9 days for the CEF-14 arm and 46.1 ± 7.9 for the CEF-21 arm).

Table 1
Patients' characteristics by treatment group

	CEF-21 ($n=178$)		CEF-14 + G-CSF ($n=185$)	
	n	(%)	*n*	(%)
Centre				
Genova	151	(85)	161	(87)
Pisa	24	(13)	20	(11)
Merate	3	(2)	4	(2)
Education (years)				
5	69	(39)	59	(32)
6–8	55	(31)	59	(32)
9–13	36	(20)	57	(31)
>13	16	(9)	9	(5)
Unknown	2		1	
Age (mean±S.D.)	52.9±9.3		52.0±9.4	
Tumour size				
pT1	106	(60)	105	(57)
pT2	65	(36)	71	(38)
pT3-4	7	(4)	9	(5)
Nodal status				
pN0	71	(40)	76	(41)
pN1-2	107	(60)	109	(59)
Surgery				
Quadrantectomy	129	(72)	126	(68)
Mastectomy	49	(27)	59	(32)

CEF-21, cyclophosphamide, epirubicin and 5-fluorouracil every 21 days; CEF-14, cyclophosphamide, epirubicin and 5-fluorouracil every 14 days; G-CSF, granulocyte-colony stimulating factor; S.D., standard deviation.

Table 2
Compliance with the psychological distress assessment by treatment groups

	CEF-21 ($n=178$)		CEF-14 + G-CSF ($n=185$)	
	n	(%)	*n*	(%)
Baseline				
Expected	178		185	
Received	155	(87)	171	(92)
Not received				
Patient refusal	1	(1)	1	(1)
Staff error	22	(12)	13	(7)
Patient lost to follow-up	–		–	
During chemotherapy				
Expected	178		185	
Received	146	(82)	155	(84)
Not received				
Patient refusal	2	(1)	4	(2)
Staff error	28	(16)	25	(14)
Patient lost to follow-up	2	(1)	1	(1)
6th month follow-up				
Expected	178		185	
Received	103	(58)	127	(69)
Not received				
Patient refusal	10	(6)	4	(2)
Staff error	54	(30)	43	(23)
Patient lost to follow-up	11	(6)	11	(6)
1st year follow-up				
Expected	175		182	
Received	113	(65)	125	(69)
Not received				
Patient refusal	9	(5)	5	(3)
Staff error	45	(26)	44	(24)
Patient lost to follow-up	8	(5)	8	(4)

CEF-21, cyclophosphamide, epirubicin and 5-fluorouracil every 21 days; CEF-14, cyclophosphamide, epirubicin and 5-fluorouracil every 14 days; G-CSF, granulocyte-colony stimulating factor.

Univariate analysis (Table 6) showed that psychological distress was significantly higher in patients experiencing some more severe toxicities, i.e. mucositis ($P=0.001$), fever ($P=0.004$), alopecia ($P=0.023$), bone pain ($P=0.003$) and fatigue ($P<0.001$).

At multivariate analysis, toxicities independently associated with a higher psychological distress were mucositis ($P=0.010$) and asthenia ($P=0.059$), while CEF-14 was still associated with a higher psychological distress (difference between arms = 2.6; P-value = 0.054).

5. Discussion

This study aimed to evaluate the impact of two different dose-intensity chemotherapy regimens on psychological distress in early breast cancer patients. The acceptable compliance obtained, ranging from 63 and 67% at the two follow-up visits to 90% at baseline, suggests an adequate reliability of the results. As well as in other studies [6,7] patients with lower education were significantly less likely to be compliant with the psychological distress evaluation. However, because there is no difference between the two arms in terms of educational level, the lower compliance in this group of patients does not affect the results of the psychological distress comparison between CEF-14- and CEF-21-treated patients.

We found that the intensive regimen has a transient worse impact on emotional well-being. During treatment, the psychological distress was higher in the CEF-14 arm (mean score 32.3 + 1.3) compared with the CEF-21 one (mean score 27.6±1.3), but no difference between the two arms was observed at 6 months after treatment. The clinical meaning of the small numerical differences in the mean scores derived from quality of life and/or psychological distress assessment instru-

Table 3
Psychological distress (mean±S.E.M.) at the four planned evaluations according to compliance at the scheduled assessments[a]

Scheduled assessments	Psychological distress inventory (PDI) (mean±S.E.M.)			
	Baseline	During CT	6th month	1st year
Baseline				
Yes	*29.4±0.8 (n=326)*	30.3±1.0 (n=277)	26.7±1.1 (n=213)	25.6±1.1 (n=212)
No	–	27.0±2.5 (n=24)	23.6±3.0 (n=17)	27.3±3.8 (n=26)
During chemotherapy (CT)				
Yes	29.7±1.0 (n=277)	*30.0±0.9 (n=301)*	26.3±1.2 (n=198)	25.1±1.1 (n=201)
No	27.7±1.8 (n=49)	–	27.8±2.7 (n=32)	29.3±3.0 (n=37)
6th month				
Yes	29.8±1.0 (n=213)	30.1±1.1 (n=198)	*26.5±1.1 (n=230)*	25.4±1.2 (n=166)
No	28.6±1.4 (n=113)	29.9±1.6 (n=103)	–	26.5±2.2 (n=72)
1st year				
Yes	29.4±1.0 (n=212)	30.6±1.1 (n=201)	26.6±1.3 (n=166)	*25.7±1.1 (n=238)*
No	29.5±1.5 (n=114)	28.8±1.7 (n=100)	26.3±2.1 (n=64)	–

S.E.M., standard error of the mean; CT, Chemotherapy.

[a] The diagonal entry (in italic) is the distribution of the PDI values using all received questionnaires. If the distribution of the missing data is at random, all the other pairs at each scheduled assessment should have the same distribution. For all the comparisons, the P values are always >0.05 (t-test for unpaired data).

Table 4
Psychological distress in the year after chemotherapy by treatment arm[a]

	Baseline		During CT		6th month		1st year	
	n	Mean±S.E.M.	*n*	Mean±S.E.M.	*n*	Mean±S.E.M.	*n*	Mean±S.E.M.
Observed values								
CEF-21	155	29.5±1.2	146	27.6±1.3	103	26.4±1.6	113	25.5±1.5
CEF-14	171	29.4±1.1	155	32.3±1.3	127	26.6±1.5	125	26.0±1.5
		($P=0.967$)		($P=0.009$)		($P=0.930$)		($P=0.799$)
Missing values estimated[b]								
CEF-21	158	29.1±1.2	158	28.0±1.2	158	25.5±1.2	158	24.5±1.1
CEF-14	174	29.5±1.1	174	31.9±1.2	174	27.4±1.2	174	26.0±1.2

CT, chemotherapy; S.E.M., standard error of the mean; CEF-21, cyclophosphamide, epirubicin and 5-fluorouracil every 21 days; CEF-14, cyclophosphamide, epirubicin and 5-fluorouracil every 14 days; PDI, Psychological Distress Inventory.

[a] $P=0.043$ (effect of treatment), $P<0.001$ (time); $P=0.104$ (interaction) in the analysis of variance for repeated measures using baseline values as a covariate.

[b] Missing values have been estimated by regressing the PDI scores at each time of evaluation on the PDI scores of the other times.

ments is uncertain [8]. In our study, the baseline scores of nearly 30 in both arms is lower than that observed using the same instrument in palliative therapy patients [5] (mean score 44) with a difference of 14 points. This indirect comparison may suggest that the difference of only 4.7 points during the treatment between the experimental and the standard arm is a minimal clinically important difference. However, although small, such a difference in psychological distress may be useful, in addition to acknowledgements of toxicity, to define the trade-offs between quantity and quality of life in patients that are candidate for adjuvant chemotherapy.

Subjective consequences of adjuvant chemotherapy in early breast cancer patients have been evaluated in two clinical trials of the International Breast Cancer Study Group carried out from 1986 to 1993 [1,6]. Data showed that chemotherapy had a transient adverse effect on quality of life, but it was minor if compared with the quality of life impairment during the process of adaptation to the disease [9]. Furthermore, quality of life has been evaluated in two recent phase III studies based on the use of dose-intensive treatment in early breast cancer patients [10,11]. In the study of Fetting and colleagues [7], the dose-intensive and standard regimens induced different types of toxicity. During treatment, quality of life declined more in the dose-intensive regimen but, by 4 months post-treatment, no difference between the two arms was observed. Nevertheless, since only marginal better breast cancer outcomes were produced by the dose-intensive regimen, the authors claim that the advantages of the experimental regimen should be carefully evaluated before choosing it over the standard treatment, which preserves a better quality of life and has a less complicated administration schedule for the patients. In the study of Levine and colleagues [8], a dose-intensive anthracycline-based regimen (cyclophosphamide, epirubicin, 5-fluorouracil (CEF)) was compared with a standard cyclophosphamide, methotrexate, 5-fluorouracil (CMF). The CEF regimen was associated with more acute toxicity compared with CMF. During treatment, quality of life was worse and decreased more quickly in the CEF arm but, by 6 months after chemotherapy, quality of life was similar in both groups. The CEF regimen was superior over CMF in terms of both relapse-free survival and overall survival and absolute benefits were 10% in 5-year relapse-free survival (53% versus 63%, $P=0.0009$) and 7% in 5-year overall survival (70% versus 77%, $P=0.03$).

Our study, evaluating the effect of chemotherapy on psychological distress, which is an important compo-

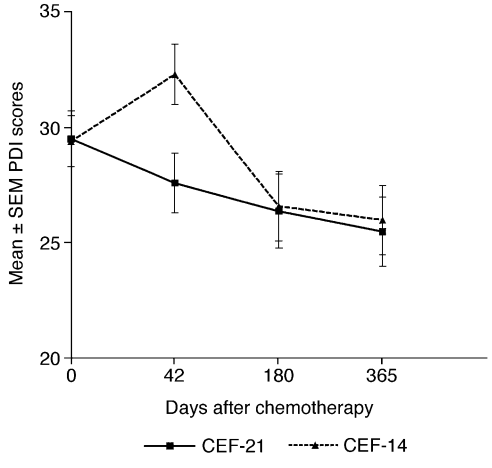

Fig. 2. Mean (+S.E.M.) Psychological Distress Inventory (PDI) scores in CEF-14- and CEF-21-treated patients at baseline (day = 0), during chemotherapy (day = 42), 6 (day = 180) and 12 (day = 365) months after chemotherapy. CEF-14 and CEF-21 = cyclophosphamide, epirubicin and 5-fluorouracil given every 14 and 21 days, respectively.

Table 5
Main toxicities (WHO) during the chemotherapy by treatment arm[a]

	CEF-21 ($n=131$)	CEF-14 ($n=146$)	
	n (%)	*n* (%)	
Anaemia			
0	128 (98)	111 (76)	
1–3	3 (2)	35 (24)	($P<0.001$)
Mucositis			
0	88 (67)	84 (58)	
1	32 (24)	37 (25)	
2–3	11 (8)	25 (17)	($P=0.033$)
Nausea/vomiting			
0	38 (29)	31 (21)	
1	51 (39)	64 (44)	
2–3	42 (32)	51 (35)	($P=0.245$)
Diarrhoea			
0	131 (100)	140 (96)	
1–3	–	6 (4)	($P=0.031$)
Fever			
0	118 (90)	125 (86)	
1–3	13 (10)	21 (14)	($P=0.259$)
Skin			
0	130 (99)	142 (97)	
1–3	1 (1)	4 (3)	($P=0.374$)
Alopecia			
1	16 (12)	12 (8)	
2	27 (21)	10 (7)	
3	88 (67)	124 (85)	($P=0.006$)
Infections			
0	128 (98)	145 (99)	
1–3	3 (2)	1 (1)	($P=0.347$)
Bone pain			
0	126 (96)	77 (53)	
1	5 (4)	32 (22)	
2–3	–	37 (25)	($P<0.001$)
Fatigue			
0	88 (67)	79 (54)	
1	35 (27)	41 (28)	
2–3	8 (6)	26 (18)	($P=0.004$)

WHO, World Health Organization; CEF-21, cyclophosphamide, epirubicin and 5-fluorouracil every 21 days; CEF-14, cyclophosphamide, epirubicin and 5-fluorouracil every 14 days.

[a] Highest toxicity before the psychological distress evaluation during the chemotherapy.

nent of quality of life, also showed that at 4–6 months post-treatment, no difference in subjective consequences was detectable between the experimental and standard arms. However, another study [12] showed that more intensive chemotherapy regimens can induce some persistent effects, such as the impairment of cognitive function.

The results of this study show that most toxicities were associated with a higher psychological distress. Patients treated with the dose-intensive regimen had a higher cumulative toxicity, which only partially explained differences in psychological distress observed between the two arms. Although worse subjective impact is an expected consequence of the higher toxicity induced by a more aggressive treatment, the relationship between toxicity and perceived quality of life is not so simple. The study by Fetting and colleagues [7], for example, showed that not all the types of toxicity were lower in the control group that evaluated quality of life as better. In particular, the dose-intensive regimen produced significantly higher grades of anaemia, nausea, stomatitis, weight loss, skin toxicity and neurotoxicity, while the standard regimen produced higher grades of leucopenia, granulocytopenia, thrombocytopenia, liver and cardiac toxicity. These results suggest that some signs and symptoms, which are clinically relevant, may have a minor impact on quality of life as perceived by the patients, while others may strongly affect subjective well-being. In our study the use of G-CSF was likely to be the cause of the higher incidence of bone pain in patients treated with CEF-14. However, at multivariate analysis bone pain was not independently associate with a higher psychological distress, while mucositis and asthenia was. Our study showed that the worse subjective impact of the dose-intensive regimen was only partly dependent on the higher toxicity induced. As a consequence, in order to better evaluate all the adverse effects of new regimens, psychological distress assessment should be routinely obtained by patients in addition to physician evaluation of toxicity. Overall costs in terms of functional and emotional well-being should be taken into account when considering a new more aggressive treatment, particularly if little benefit in terms of survival is expected. Any difference in quality of life has to be evaluated against any difference in efficacy. If a more intense therapy is shown to be more effective, then there should be a specific analysis based on the usefulness of the quality of life data. If it is equally or less effective compared with the standard therapy, quality of life data may be useful in deciding whether it should be abandoned.

Table 6
Psychological distress and chemotherapy toxicity

	n	During chemotherapy	
		Adjusted means±S.E.M.[a]	
Anaemia			
0	239	30.0±0.7	($P=0.257$)
1–3	38	32.5±1.3	
Mucositis			
0	172	28.4±0.9	
1	69	32.5±1.3	
2–3	36	35.2±1.9	($P=0.001$)
Nausea/vomiting			
0	69	30.2±1.4	
1	115	28.9±1.1	
2–3	93	32.1±1.2	($P=0.138$)
Diarrhoea			
0	271	30.2±0.7	
1–3	6	35.8±4.7	($P=0.232$)
Fever			
0	243	29.6±0.7	
1–3	34	35.5±1.9	($P=0.004$)
Skin			
0	272	30.2±0.7	
1–3	5	35.7±5.1	($P=0.292$)
Alopecia			
1	28	25.4±2.2	
2	37	28.4±1.9	
3	212	31.3±0.8	($P=0.023$)
Infections			
0	273	30.3±0.7	
1–3	4	30.2±5.8	($P=0.993$)
Bone pain			
0	203	28.9±0.8	
1	37	33.9±1.9	
2–3	37	34.4±1.9	($P=0.003$)
Fatigue			
0	167	29.0±0.9	
1	76	29.9±1.3	
2–3	34	37.5±1.9	($P<0.001$)

[a] Psychological Distress Inventory (PDI) scores during the chemotherapy adjusted for the baseline PDI values.

In conclusion, our study shows that a dose-intensive adjuvant chemotherapy induced a higher, although transient, psychological distress in early breast cancer patients. Such a higher psychological distress is only partly explained by the higher toxicity induced by the dose-intensive regimen, because there is only a moderate correlation between clinician-rated toxicity and subject-rated distress. Therefore, both patient-rated psychological distress and clinician-rated toxicity should be assessed in randomised clinical trials of treatment.

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