APPENDIX

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A Pilot Study of Accelerated Cyclophosphamide, Epirubicin and 5-Fluorouracil Plus Granulocyte Colony Stimulating Factor as Adjuvant Therapy in Early Breast Cancer

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32 consecutive early breast cancer patients were treated to evaluate the feasibility of an accelerated CEF regimen (cyclophosphamide 600 mg/m², epirubicin 60 mg/m² and 5-fluorouracil 600 mg/m²) given intravenously every 2 weeks for six cycles together with granulocyte colony stimulating factor, 5 μg/kg/day subcutaneously from day 4 to day 11. One hundred and eighty two out of 192 planned cycles (95%) were administered. Toxicity was mild: no cases of grade IV non-haematological toxicity and only one episode of grade IV granulocytopenia were observed. Delays or dose reductions of anti-neoplastic drugs occurred in 14 cycles (7.7%). The mean duration of six cycles of treatment was 71 days (planned 70) and 93% of average planned dose intensity was actually administered. The short course CEF therapy is a feasible, well tolerated outpatient chemotherapy regimen, allowing a 46% increase in dose intensity compared with a standard CEF regimen given every 3 weeks. A randomised study comparing this regimen to a standard CEF regimen is now in progress in early breast cancer patients.

Key words: dose intensity, breast cancer, adjuvant chemotherapy, G-CSF
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INTRODUCTION

ONE EXTENSIVELY studied and debated chemotherapy variable over the last few years has been dose intensity. Retrospective analyses indicate that treatment outcome of early breast cancer patients may be affected both by the total dose of chemotherapy actually administered [1] and by the dose intensity of the utilised regimen [2]: the higher the dose or the dose intensity, the better the outcome. However, until now, no randomised study has proven that high dose intensity chemotherapy regimens are better than standard.

Actually, the most important limiting factor hindering the administration of higher than standard dose intensity is myelotoxicity. Recently, some haemopoietic colony stimulating factors (CSFs) have proven able to reduce the haematological toxicity of some standard dose regimens [3, 4]. Moreover, several phase I/II studies utilising granulocyte (G-CSF) or granulocyte–

macrophage colony stimulating factor (GM-CSF) indicate that these CSFs allow doses to be increased [5, 6] and/or intervals between cycles shortened in advanced breast cancer [6, 7].

Anthracyclines have been shown to be the most active drugs in metastatic breast cancer [8] and, furthermore, the results provided by some clinical trials [9, 10] also suggest a possible important role in an adjuvant setting. Based on this and on our previous experience in both metastatic [7, 11] and early breast cancer [12], the CEF regimen (cyclophosphamide, epirubicin, 5-fluorouracil) was chosen to evaluate the possibility of increasing dose intensity. Of the two methods of increasing dose intensity, i.e. to increase the doses themselves or to reduce the intervals between cycles, we have pursued the latter on the grounds that the use of G-CSF or GM-CSF, also in standard dose regimens, induces an earlier leucocyte nadir followed by a more rapid recovery than treatment without CSFs [3, 6, 7], and could allow an accelerated chemotherapy. Therefore, the main objective of our study was to evaluate the feasibility of an accelerated CEF regimen administered in an out-patient setting that allows a 50% increase in dose intensity with respect to a standard CEF regimen given every 3 weeks.

PATIENTS AND METHODS

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 study if they had involved axillary nodes or were node-negative but with high risk of recurrence. Risk was defined as the presence of one or more of the following criteria: age $\leq$35 years, negative oestrogen (ER) and progesterone receptor (PgR) status, tumour size $\geq$3 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 (WBC) count $\geq$3000/mm^3, platelet count $\geq$100 000/mm^3], adequate hepatic 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 conserving surgery, previous or concomitant malignancy (except curatively treated skin or cervix carcinoma), medical condition precluding anthracycline treatment, drug-requiring psychiatric illness.

Biochemical tests were performed before entry to the study and before cycles three and six. In order to evaluate the haematological toxicity at nadir, a complete blood test with white cell differential and platelet count was taken twice a week. The toxicity was recorded according to the World Health Organization scale [13].

The study was accepted by the Protocol Review Committee of the Istituto Nazionale per la Ricerca sul Cancro (IST). Institutional review board-approved informed consent was obtained from all patients prior to study entry. The study was carried out at the Istituto Nazionale per la Ricerca sul Cancro of Genova.

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Treatment plan

The chemotherapy regimen consisted of six cycles of CEF (cyclophosphamide 600 mg/m^2, epirubicin 60 mg/m^2, 5-fluorouracil 600 mg/m^2). All drugs were administered intravenously on day 1. Cycles were repeated every 2 weeks if WBC were $\geq$3000/mm^3 and platelets were $\geq$100 000/mm^3. G-CSF (5 μg/kg/day) was subcutaneously self-administered from day 4 until day 11, from cycles one to five. After cycle six, the G-CSF was not given. G-CSF treatment was temporarily interrupted if the WBC count was more than 20 000/mm^3. Antibiotic prophylaxis with oral ciprofloxacin 500 mg twice per day was planned for patients with grade IV leucopenia.

In patients subjected to breast-conserving surgery, the radiotherapy on residual breast was administered concurrently or after the end of chemotherapy. The radiotherapy dose was 50 Gy in 5 weeks; if the tumour was >1 cm, a boost of 10 Gy was performed.

Drug dosage modification

On day 1 of the cycle, in the presence of grade $\geq$II leucopenia or grade I–II thrombocytopenia, treatment was delayed until recovery; in the presence of grade III–IV leucopenia associated with grade I–II thrombocytopenia or grade III–IV thrombocytopenia alone, chemotherapy was delayed, and in subsequent cycles the individual doses of the three drugs were reduced by 25%. A maximum treatment delay of up to 2 weeks was permitted to allow for recovery from haematological toxicity.

The guidelines for dosage modification due to non-haematological toxicity, except hair loss and nausea or vomiting, were the following: in the presence of grade II toxicity, the treatment was delayed until recovery; in the presence of grade III–IV, the treatment was delayed, and in subsequent cycles the doses of the three drugs were reduced by 25%.

Dose intensity calculation

Dose intensity was defined as the amount of drug (mg/m^2) administered per unit time (week). The planned dose intensity was 300 mg/m^2/week for cyclophosphamide and 5-fluorouracil, and 30 mg/m^2/week for epirubicin. The doses of the three drugs being uniformly reduced in the case of toxicity, the dose intensity of all three drugs corresponded to the dose intensity of any one drug. Hence, only the dose intensity of cyclophosphamide was calculated. For patients who received fewer than six cycles, the duration of therapy was calculated on the basis of the projected duration (12 weeks), and the total dose was the dose actually given in received cycles of chemotherapy (i.e. assigning a dose = 0 for cycles not administered). Actually given dose intensity was calculated by dividing the total amount of drug administered by the time taken. In order to compare the administered dose intensity of this regimen with other similar anthracycline-based regimens, we calculated the average relative dose intensity (ARDI) as previously described [14] by utilising a common CAF (cyclophosphamide, doxorubicin, 5-fluorouracil) program [15] as a standard regimen. In this comparison, we presumed the same activity of doxorubicin and epirubicin [16, 17] and of cyclophosphamide given intravenously or orally.

RESULTS

From March to October 1992, 32 patients entered the study. Main patients' characteristics are shown in Table 1. 21 of 32 patients (66%) had radiotherapy to the residual breast after conservative surgery, whilst the others had undergone modified radical mastectomy. Overall, 182 out of 192 planned cycles

Table 1. Patients' characteristics

	No. of patients	%
Age <50/≥50 years	13/19	41/59
Pre/postmenopausal	12/20	38/62
Tumour size		
T1	14	44
T2	16	50
T3	2	6
Nodal status		
N0	8	25
N1–3	13	41
N≥4	11	34
Grading		
1	4	12
2	14	44
3	14	44
ER+/ER−	16/10	50/31
Inadequate material	6	19
PgR+/PgR−	14/11	44/34
Inadequate material	7	22

Table 2. Non-haematological toxicity

	Patients No. (%)	Cycles No. (%)
Nausea-vomiting		
I/II	21 (66)	50 (27)
III	3 (9)	3 (2)
Stomatitis		
I/II	10 (31)	15 (8)
III	3 (9)	7 (4)
Alopecia	32 (100)	—
Liver II	1 (3)	1 (0.5)
Skin I/II	1 (3)	1 (0.5)
Bone pain	9 (28)	12 (6)
Flu-like syndrome	1 (3)	1 (0.5)

(95%) were administered, 66 cycles (36%) concurrently with radiotherapy. 27 patients (84%) completed six planned cycles of chemotherapy. 5 patients (16%) stopped chemotherapy: 3 due to psychological reasons (2 after cycle four and 1 after cycle three); 1 patient refused transfusion at cycle 6 in the presence of symptomatic grade II anaemia; the last patient developed grade II liver toxicity (i.e. alanine aminotransferase = 105 U/l) after the fourth cycle, and stopped on the decision of the physician.

Non-haematological toxicity is shown in Table 2. Ninety-four cycles (52%) were given without any toxicity. No grade IV toxicity was observed. Grade III toxicities were nausea and vomiting in 9% of patients, and stomatitis in 9% of patients, occurring in 10/182 cycles (5%). G-CSF-related toxicities were flu-like syndrome in 1 patient, bone pain in 28% of patients and skin reaction at the injection site in 1 patient.

Haematological toxicity was recorded at nadir in the first 16 patients (50%) (Table 3). Due to the low toxicity observed in these patients, blood count was performed only at day 1 of each cycle in the remaining 16 subjects. Grade I and II granulocytopenia was observed in 5 patients (31%) and in 13 cycles (15%); grade III in 2 patients (12.5%) and in four cycles (5%); only one episode of grade IV granulocytopenia lasting 5 days was recorded, and no patient developed febrile neutropenia. No grade III/IV thrombocytopenia was observed, while grade I/II occurred in 9 patients (56%) and 16 cycles (18%). Haemoglobin values, evaluated in all 32 patients at day 1 of the cycle, progressively declined: the mean value fell from 13.0 g/dl (range 9.3–15.3) at baseline to 10.8 g/dl (range 8.8–12.7) at the sixth cycle. Overall, 16 patients (50%) suffered from grade I anaemia, and 4 patients (12.5%) from grade II. 3 patients (9%) required red blood cell transfusions for a total of seven units.

Seven cycles (4%) were delayed, two due to patient request and five due to toxicity: grade II granulocytopenia lasting 10 days (one cycle), grade II thrombocytopenia lasting 6 days (three cycles) and 3 days (one cycle). The five cycles delayed due to haematological toxicity were administered concurrently with radiotherapy. A 25% dose reduction was performed in seven cycles (4%) due to grade III mucositis.

The mean delivered total dose of cyclophosphamide was 5760 mg (range 3000–6960). The mean duration of six cycles of treatment was 71 days (range 69–92). 5 patients stopping

Table 3. Haematological toxicity at nadir

	Cycle 1	2	3	4	5
Mean nadir × 1000/mm³					
Granulocytes (±S.D.)	3.1 (1.7)	2.6 (1.5)	3.4 (2.4)	4.0 (2.3)	2.3 (0.9)
Range	0.85–7.5	0.72–5.5	1.6–8.4	0.35–8.3	1.7–3.7
Platelets (±S.D.)	159 (51)	157 (66)	133 (46)	147 (54)	148 (51)
Range	71–239	54–289	71–214	74–217	79–221
Median day of granulocyte's nadir	4	6	7	7	5
Range	2–10	3–20	2–10	3–10	3–8

treatment before cycle six were excluded from this latter calculation in order to avoid an erroneously reduced duration resulting from the fewer number of cycles received by these patients. The mean cyclophosphamide dose intensity actually given, calculated in all 32 patients, was 278 mg/m^2 week (range 238–319), which corresponded to 93% of the planned dose intensity. If compared to CEF, at the same doses and given every 3 weeks, this corresponded to a 46% dose intensity increase.

DISCUSSION

The primary objective of this study was to determine the feasibility of a CEF regimen administered every 2 weeks with the support of G-CSF. Accelerated CEF appears to be safe and feasible with low toxicity. This regimen was administered in an out-patient setting and no admissions were necessary. No grade IV non-haematological toxicity was observed, and a minority of patients, only 9%, suffered from grade III nausea/vomiting and mucositis. Noteworthy is that only 22/182 cycles (12%) were associated with epithelial mucositis, despite the acceleration of a drug such as epirubicin whose main toxicities include stomatitis. Haematological toxicity was very mild. Only 1 patient had grade IV granulocytopenia lasting 5 days. The most frequent haematological toxicity was grade I/II anaemia which occurred in 62.5% of patients, and caused interruption of treatment in 1 patient. Moreover, as reported in other studies using accelerated chemotherapy [7, 18], the anaemia progressively worsened with increasing treatment cycles. G-CSF toxicity was mild and was not cause for the interruption of treatment in any case.

Treatment compliance was good and similar to that reported in other adjuvant studies [10, 19]: 16% of patients did not complete the six planned cycles. Treatment delays or dose reductions were performed only in 14 cycles (7.7%).

Treatment duration and the number of cycles administered seem to be two critical factors in adjuvant therapy. As reported by NSABP (National Surgical Adjuvant Breast and Bowel Project), a short course of chemotherapy including an anthracycline, e.g. 2 months of doxorubicin and cyclophosphamide (four cycles), is as effective as 6 months of CMF (six cycles), and is associated with a better quality of life [20]. In contrast, another study [21] suggested that a regimen lasting less than 3 months may be insufficient; however, the negative results of the 3-month arm in this study can be traced to several factors other than the short duration of therapy. The study was stopped on the basis of an unplanned interim analysis. The total dose of the short-course CMF-based chemotherapy was nearly 50% of a standard CMF regimen administered for six cycles. The duration of CMF-based chemotherapy was not 3 but 2 months: weekly low dose doxorubicin was utilised in the last month. Moreover, it has recently been demonstrated that the sequential use of doxorubicin after CMF provides no better results than CMF alone [22].

Therefore, taking into account data from both a randomised study, indicating that treatment beyond six cycles of CMF provides no additional benefit [23], and a retrospective study, suggesting that patients who received fewer than four cycles of combination chemotherapy had a reduced disease-free survival [15], our programme enables the administration of six cycles of treatment over a relatively short time: 71 days on average.

Our regimen allows a delivered dose intensity higher than that achievable with other standard breast chemotherapy regimens [15, 24] or with some moderately intensified regimens recently reported as pilot studies [25, 26]. To compare these studies, we calculated the ARDI, taking as the standard regimen the M.D. Anderson CAF which has been extensively used in adjuvant breast cancer [15]. We also included the Eastern Cooperative Oncology Group (ECOG) CAF regimen, used in metastatic breast cancer, in which dose intensity was calculated only in the first three cycles [24], since this regimen is now widely used in adjuvant settings [27]. The actual ARDI of our regimen was 1.41, that of the Seattle group [25] 1.25, of the Ontario group [26] 1.07 and of the ECOG group [24] 1.04.

In view of these findings, we have started a randomised study comparing six cycles of this accelerated CEF with a standard CEF at the same doses, but given every 3 weeks, to verify the clinical impact of a planned 50% dose intensity increase in early breast cancer patients.

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Tropisetron Compared With a Metoclopramide-based Regimen in the Prevention of Chemotherapy-induced Nausea and Vomiting

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This randomised, open, parallel group study compared the antiemetic efficacy and tolerability of tropisetron with metoclopramide plus lorazepam in 102 patients receiving a first course of non-cisplatin-containing chemotherapy. Control of acute vomiting by tropisetron was significantly superior to that of the metoclopramide regimen, with total control (no vomiting) in 45% of 51 patients in the tropisetron group compared with 22% of 51 patients in the metoclopramide group ($P = 0.013$); total and partial control (< 5 vomits) occurred in 67 and 47% of patients, respectively ($P = 0.044$). The incidences of acute nausea and of delayed nausea and emesis were similar in the two treatment groups. Both tropisetron and metoclopramide were well tolerated; no adverse effects were attributed to tropisetron administration with the exception of headache. One patient in the metoclopramide group reported confusion and tremor thought to be related to the antiemetic therapy. Tropisetron is an effective and well-tolerated agent in the prevention of chemotherapy-induced vomiting. The control of acute nausea was similar in the two treatment groups, but tropisetron was superior to a metoclopramide-based regimen in the control of acute vomiting.

Key words: tropisetron, metoclopramide, lorazepam, chemotherapy-induced emesis, comparative study
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INTRODUCTION

NAUSEA AND vomiting are among the most frequent and distressing adverse effects of cancer chemotherapy. Failure to control chemotherapy-induced emesis has a detrimental effect upon patients' quality of life, increasing the likelihood of non-compliance with, or refusal of anticancer treatment [1]. Antiemetic regimens, including high doses of metoclopramide and corticosteroids, can control chemotherapy-induced emesis, but their effectiveness may be offset by poor tolerability [2, 3].

The 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists are a new class of antiemetic agents, of which tropisetron (ICS 205-930, Navoban®; Sandoz Pharma Ltd, Basle, Switzerland) is a member. Early non-comparative clinical studies have shown tropisetron to be effective and well tolerated in patients receiving