Feasibility of a dose-intensive CMF regimen with granulocyte colony-stimulating factor as adjuvant therapy in premenopausal patients with node-positive breast cancer

AME Bos¹, H de Graaf², EGE de Vries¹, H Piersma³ and PHB Willemse¹

¹Division of Medical Oncology, Department of Internal Medicine, University Hospital, PO Box 30 001, 9700 RB Groningen, The Netherlands; ²Department of Internal Medicine, Medical Center Leeuwarden, Leeuwarden, The Netherlands; ³Department of Internal Medicine, Martini Hospital, Groningen, The Netherlands

Summary Our aim was to study the feasibility of an intensified intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) schedule with the aim to escalate dose intensity (DI). Twenty-three premenopausal breast cancer patients received 6 cycles of adjuvant CMF intravenously on days 1 and 8 every 3 weeks and granulocyte colony-stimulating factor days 9–18. Endpoints were DI and toxicity. Twenty-one out of 23 patients (91%) received the projected total dose and reached ≥85% of the projected DI. Nine patients received the planned schedule without delay. Thirteen patients (57%) were treated for infection and four patients (17%) were hospitalized for febrile neutropenia. Twelve patients received red blood cell transfusions (52%). Radiation therapy (n = 6) had no adverse impact on dose intensity or haematological toxicity. This dose-intensified CMF schedule was accompanied by enhanced haematological toxicity with clinical sequelae, namely fever, intravenous antibiotics and red blood cell transfusions, but allows a high dose intensity in a majority of patients. © 2000 Cancer Research Campaign

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Cyclophosphamide, methotrexate and 5-fluorouracil (CMF) is widely used as a chemotherapy combination for the adjuvant treatment of breast cancer. The ‘classical’ CMF regimen comprises 6 cycles of oral cyclophosphamide (100 mg m⁻² day⁻¹) days 1–14 with intravenous (i.v.) methotrexate (40 mg m⁻²) and i.v. 5-fluorouracil (600 mg m⁻²) on days 1 and 8, repeated every 28 days (Bonadonna and Valagussa, 1981). To improve the therapeutic index, the dosages, schedule and route of administration of CMF have been widely varied. Several trials have suggested that relapse-free survival and overall survival not only depend on the total dose of the cytotoxic drugs actually administered, but the more so on the dose intensity, i.e. the amount of drug given per unit of time (Bonadonna and Valagussa, 1981; Hryniuk and Bush, 1984; Hryniuk and Levine, 1986; Hryniuk et al, 1987; Tannock et al, 1988; Ang et al, 1989; Engelsman et al, 1991; Wood et al, 1994).

Based on the assumptions that compliance with oral cyclophosphamide would be less than when the drug was given i.v. and that variability in absorption of cyclophosphamide by the oral route could lead to variable bio-availability, several studies have used i.v. CMF schedules. A potential advantage of the i.v. regimens is the easier possibility of a combination with a haematopoietic growth factor such as granulocyte colony-stimulating factor (G-CSF). G-CSF stimulates the recovery of granulocytes after chemotherapy. G-CSF has been used to enhance dose intensity by shortening the interval between cycles or by increase in dosage (Bronchud et al, 1989; Neidhart et al, 1991; Lieschke and Burgess, 1992; Biesma et al, 1992; De Graaf et al, 1996; Ribas et al, 1996).

The aim of the present prospective study was to evaluate the feasibility of a regimen with an intensified i.v. CMF schedule supported by G-CSF and administered every 3 weeks, reaching a projected dose intensity (DI) of 143% compared to ‘classical’ CMF.

PATIENTS AND METHODS

Eligible were premenopausal women who were considered for adjuvant chemotherapy with CMF. Primary treatment consisted of a modified radical mastectomy or breast-conserving surgery. Patients were ineligible if they had renal impairment (serum creatinine level > 120 μmol l⁻¹), abnormal liver function (bilirubin level > 25 mmol l⁻¹) or abnormal baseline marrow reserve (leucocyte count < 3.0 × 10⁹ l⁻¹, platelet count < 150 × 10⁹ l⁻¹).

Patients received cyclophosphamide 750 mg m⁻², methotrexate 40 mg m⁻² and 5-fluorouracil 600 mg m⁻², all i.v. on days 1 and 8, repeated every 21 days, for a total of 6 cycles. The administration of the chemotherapy on days 1 and 8 were defined as two separate courses (A and B), so patients received a total of 12 courses. G-CSF (Neupogen, Roche, Mijdrecht, The Netherlands) was administered in a dose of 300 μg subcutaneously once a day on days 9–18 of each cycle. Blood counts were collected on days 1 and 8 before i.v. administration of the chemotherapeutic drugs. The chemotherapy was administered if the leucocyte count was > 2.5 × 10⁹ l⁻¹ on day 1 or > 1.0 × 10⁹ l⁻¹ on day 8 and if the platelet count was > 75 × 10⁹ l⁻¹ on day 1 and > 50 × 10⁹ l⁻¹ on day 8. These non-conventional thresholds, which were allowed by the support
of G-CSF, were applied to minimize the delay of treatment due to myelosuppression and to achieve a dose-intensive CMF regimen. In the event of myelosuppression on the planned day of drug administration, treatment was delayed for 1 week. No dose reductions were scheduled for nadir values or intercurrent fever. Red blood cell transfusion was administered for haemoglobin values < 6.5 mmol l⁻¹.

Radiation therapy was administered in case of involvement of more than three positive lymph nodes, extranodal tumour growth, multifocal tumour or breast lymphangitis. Radiotherapy was administered concomitantly with CMF chemotherapy.

Toxicity was recorded using the WHO criteria (WHO, 1979). The total dose of the chemotherapeutic drugs was expressed as the percentage of the actual amount administered divided by the projected amount, in which each drug was given equal value. The DI was given as a percentage of the total dose administered per unit time (weeks), divided by the actual duration of treatment. The study was approved by the Medical Ethical Committee and all patients gave informed consent.

The χ² test (Mantel–Haenszel) was used for statistical analysis with the exception of the analysis of the leucocyte counts related to Figure 1. For this purpose Friedman’s test (two-way rank analysis) was used together with Duncan’s test for correction of multiple comparisons. The confidence intervals were 95%.

RESULTS

Patient characteristics

Over a period of 1 year, 23 women entered the study. Twenty-one patients had undergone a modified radical mastectomy and two patients breast-conserving surgery. Twenty-two patients had lymph node involvement, two had more than four positive nodes, one patient was node-negative. Six patients received loco-regional radiation therapy, including two with breast conserving therapy. The median start of the chemotherapy was 19 days (range 14–48) and of radiotherapy 64 days after surgery (range 43–78 days). The patients’ characteristics are shown in Table 1.

Table 1  Patient characteristics (n = 23)

| Age (years) | Median 44 | Range 26–55 |
| Primary tumour | pT1 4 | pT2 19 |
| Axillary lymph nodes examined | Median 10 | Range 1–16 |
| Axillary lymph nodes involved | Median 1 | Range 1–8 |
| Surgical treatment | Modified mastectomy 21 |
| Breast-conserving surgery | 2 |
| Locoregional radiotherapy | 6 |

Dose intensity

Two patients did not receive all courses of chemotherapy. One patient had fever with leukopenia and skipped course 4B. Another patient did not receive the last course (6B) due to haematological toxicity. A total of 274 out of 276 courses were completed. Table 2 shows the actually achieved DI as a percentage of the projected DI (range 78–100%) and the actually achieved DI compared to ‘classical’ CMF (range 111–143%). In 21 patients the actually delivered DI was ≥ 85% of the projected DI, which is the equivalent of ≥ 120% compared to ‘classical’ CMF.

Delay of treatment

Out of these 23 patients, ten received all treatment as planned; delay of treatment occurred in 13 patients (57%). A total of 17 courses out of 274 (6.2%) were delayed for a median of 1 week (range 1–3 weeks). The total delay was 23 weeks (5.6%) on a projected total treatment duration of 414 weeks for all patients. The reasons for delay of chemotherapy are listed in Table 3. Delay for insufficient marrow recovery and for fever and infection were the most important causes.

Toxicity

Figure 1 shows the median leucocyte count with ranges at the start of the courses. Over time, the median leucocyte count on day 8 declined, suggesting cumulative toxicity. Moreover, the absolute increase of leucocytes during G-CSF administration (i.e. the reserve-capacity) declined. The relative increase of leucocytes related to the nadir in these cycles, however, were not different.

Table 2  Actually achieved dose intensity (DI) compared to ‘classical’ CMF regimen

| Achieved dose intensity (% of projected DI) | Number of patients | Achieved DI compared to ‘classical’ CMF |
|--------------------------------------------|--------------------|----------------------------------------|
| DI 100%                                   | 9                  | DI 143%                                |
| DI 85%–100%                               | 12                 | DI 120–143%                            |
| DI < 85%                                  | 2                  | DI < 120%                              |
| Median DI: 95% (range 78–100%)            | Total: 23          | Median DI: 135% (range 111–143%)       |
Overall, these changes indicate a gradual fall in bone marrow reserve capacity.

Thirteen out of 23 patients (57%) were at least once (range 1–3) affected by fever grade 2 (temperature > 38.0°C) and were treated by oral or i.v. antibiotics. Eleven patients (48%) were treated by oral antibiotics (infection grade 2). Four out of 23 patients (17%) had fever with neutropenia and were admitted for i.v. antibiotics (infection grade 3). The time to the first episode of infection is shown in Figure 2. One prophylactic transfusion of platelets was given for grade IV thrombocytopenia without bleeding. Red blood cell (RBC) transfusions were administered to 12 patients (52%) at a median value of haemoglobin of 5.5 mmol l⁻¹. The median number of transfusions was 3 units (range 2–6), for a total of 45 units. Figure 3 shows the cumulative probability of the first RBC transfusion during treatment.

The main toxicity related to the use of G-CSF was mild bone pain in seven patients (mainly in the first two cycles during the last days of G-CSF) and musculoskeletal pain in two patients and was not a reason to withhold its administration.

### DISCUSSION

We have studied the feasibility of an accelerated CMF schedule aiming to reach a higher dose intensity. The dose-intensification was achieved by shortening the cycle interval and by slightly increasing the dose of cyclophosphamide, supported by G-CSF. The dose intensity for cyclophosphamide was 500 mg m⁻² week⁻¹ i.v., a factor 1.43 compared to the ‘classical’ CMF regimen (350 mg m⁻² week⁻¹ orally). The dose intensity for methotrexate and 5-fluorouracil was 133% compared to the oral schedule. With this modified schedule, the median actually achieved dose intensity was 135% compared to the ‘classical’ CMF. Recently, Goldhirsch et al concluded that the many variations in CMF regimens did not improve results (Goldhirsch et al, 1998a, 1998b). However, several studies have suggested that a higher dose or dose intensity of chemotherapy may improve disease-free and overall survival (Bonadonna and Valagussa, 1981; Hryniuk and Bush, 1984; Hryniuk and Levine, 1986; Hryniuk et al, 1987; Tannock et al, 1988; Ang et al, 1989; Engelman et al, 1991; Wood et al, 1994). Bonadonna and Valagussa (1981) suggested after a retrospective analysis, that the effectiveness of adjuvant CMF depends on the total dose actually administered. CMF was only useful when given ≥ 85% of the planned dose (Bonadonna and Valagussa, 1981). Wood et al reported the results of a prospective, randomized trial of adjuvant cyclophosphamide, doxorubicin and 5-fluorouracil in three dose levels (Wood et al, 1994). The women treated with a moderate or high dose intensity had a significantly longer disease-free and overall survival than those treated with a low dose intensity. Tannock et al reported a reduction in response rate and overall survival in patients who received the lower (50%)
dose arm compared to the standard intravenous CMF in metastatic
disease (Tannock et al, 1988).

An advantage of giving cyclophosphamide i.v. is the possibility to
start G-CSF immediately after the second i.v. dose from day 8
onwards and thus shorten the interval between the cycles. Several
studies examining the route of administration have been published
(Engelsman et al, 1991; Lindeman et al, 1992). An EORTC random-
ized study has compared ‘classical’ CMF with i.v. CMF (cyclo-
phosphamide 600 mg m⁻², methotrexate 40 mg m⁻² and 5-fluorouracil
600 mg m⁻², all i.v. on day 1) in 254 eligible patients with metastatic
breast cancer (Engelsman et al, 1991). The response rate after ‘clas-

We conclude that this modified i.v. CMF regimen carries
enhanced haematological toxicity with clinical sequelae (namely
fever, i.v. antibiotics and many RBC transfusions), but allows a
high dose intensity in a majority of patients. This dose-intensive
CMF schedule could be the basis for a randomized phase III study
to compare with ‘classical’ CMF. Such a study should also
examine dose-intensity, toxicity, cost and quality of life. It should
be possible to use erythropoietin for treatment of anaemia and
prophylactic antibiotics to prevent infections. Also, repeated
peripheral stem cell support could be used to achieve high dose
intensity with less haematological toxicity.

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