The feasibility of classical cyclophosphamide, methotrexate, 5-fluorouracil (CMF) for pre- and post-menopausal node-positive breast cancer patients in a Belgian multicentric trial: a study of consistency in relative dose intensity (RDI) and cumulative doses across institutions

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Background: Classical cyclophosphamide, methotrexate, 5-fluorouracil (CMF) including oral cyclophosphamide is still considered an important adjuvant chemotherapy regimen in patients with early breast cancer (BC). Concern has been raised regarding the feasibility of this regimen, especially in post-menopausal patients.

Patients and methods: 254 pre- and post-menopausal node-positive BC patients aged ≤70 years received six cycles of CMF in the context of a Belgian multicentric phase III trial of adjuvant chemotherapy. CMF dose and schedule were as follows: cyclophosphamide 100 mg/m² p.o. on days 1 to 14, methotrexate 40 mg/m² intravenously (i.v.) on days 1 and 8, 5-fluorouracil 600 mg/m² i.v. on days 1 and 8; cycles q. 28 days. The relative dose intensity (RDI) was calculated as the ratio between the delivered DI and the planned DI. We also analysed the RDI in two subgroups of patients with age ≥50 years or <50 years.

Results: Overall, the percentage of patients ending the six cycles of the planned CMF regimen was 90%. The mean RDI achieved in the population of 254 patients was 90% (range 8% to 129%). The subgroup analysis of patients aged ≥50 years and <50 years showed that 81% and 76% of patients, respectively, received ≥80% of the planned chemotherapy dose intensity (\(P = 0.33\)). No statistically significant difference was found between the percentage of patients who received a RDI <80% and the participating institutions (\(P = 0.50\)).

Conclusions: The classical CMF regimen was a feasible regimen in the context of a multicentric trial, in which academic institutions as well as community hospitals participated. No substantial differences in RDI and cumulative doses were found in relation to a patient’s age and the participating institution.

Key words: adjuvant chemotherapy, breast cancer, classical CMF, feasibility

Introduction

The schedule of the classical cyclophosphamide, methotrexate, 5-fluorouracil (CMF) regimen was designed in order to mimic the highly successful MOPP (mechlorethamine, vincristine, procarbazine and prednisone) regimen developed in the mid 1960s for use in the treatment of advanced Hodgkin’s disease [1]. The classical CMF regimen consists of cyclophosphamide 100 mg/m² orally on days 1 to 14, methotrexate 40 mg/m² intravenously (i.v.) on days 1 and 8, and 5-fluorouracil 600 mg/m² i.v. on days 1 and 8, with all drugs restarted on day 29.

Based on the encouraging response rates of 40–50% observed with classical CMF in previously untreated metastatic breast cancer patients, the Milan group launched their first adjuvant trial in patients with node-positive breast cancer more than 25 years ago [2, 3]. The results of this trial had a major impact on the standard of care for breast cancer patients. Since their publication, adjuvant polychemotherapy has been used for subgroups of women with early-stage breast cancer, and has been shown to improve both disease-free survival (DFS) and overall survival (OS) [4, 5].
Concern has been raised regarding the feasibility of delivering an acceptable dose intensity of this regimen. In the Milan trials, in the sub-group of postmenopausal women, a significant proportion of patients had nausea, vomiting and loss of appetite, which led to a drop of relative dose intensity [3, 6]. Retrospectively, the same group demonstrated that a drop of RDI below 65% of the planned dose intensity compromised the efficacy of this regimen in the adjuvant setting. Another source of concern is that, for bone marrow recovery, it may be preferable not to use cyclophosphamide continuously for 2 weeks and not to repeat methotrexate and 5-fluorouracil (5-FU) on day 8 [10].

In order to circumvent these problems, numerous modifications of dose and schedule of the classical CMF regimen have been made [7–9]. These regimens replace the oral administration of cyclophosphamide with the i.v. route and in some cases do not administer the ‘day 8’ of methotrexate and 5-FU. The ‘modified’ or i.v. CMF regimens most often have a lower dose intensity and dose density compared with the classical schedule.

The CMF variants are widely used but have never been compared in the adjuvant setting with the classical CMF regimen.

Of concern is the result of a European Organization for the Research and Treatment of Cancer (EORTC) trial in postmenopausal women with metastatic breast cancer, in which the classical CMF was compared with a modified CMF (cyclophosphamide 600 mg/m² i.v. on day 1, methotrexate 40 mg/m² i.v. on day 1 and 5-FU 600 mg/m² i.v. on day 1, repeated every 21 days). This EORTC multicentric phase III trial found an inferior response rate, time to progression and OS for patients receiving the modified CMF [10]. In addition, it has been shown that only in the trials in which the classical CMF regimen has been used was it possible to demonstrate a benefit when CMF was added to tamoxifen in post-menopausal patients with node-positive, oestrogen receptor (ER)-positive tumours [11].

Because of this background suggesting an increased efficacy of classical CMF when compared with ‘modified’ CMF regimens, and because of existing and unproven concerns related to the feasibility of the classical CMF regimen, we have decided to systematically evaluate the feasibility of this treatment in the context of a multicentric phase III trial of adjuvant chemotherapy.

From 1988 to 1996, a Belgian multicentric adjuvant trial [12] recruited pre- and post-menopausal node-positive breast cancer patients who were randomly treated with a full-dose epirubicin/cyclophosphamide (HEC) regimen or with CMF or with a low-dose epirubicin/cyclophosphamide (EC) regimen. Sixteen different institutions participated in this study.

The primary end-point of the present retrospective analysis was to assess if the classical CMF relative dose intensity was modified according to the participating institution and patient’s age. A secondary end-point was to evaluate DFS in relation to the classical CMF relative dose intensity (RDI).

Materials and methods

Patients

Patients <70 years of age with surgically resected, histologically confirmed, breast carcinomas were eligible for study participation. At least one out of a minimum of eight resected ipsilateral axillary nodes had to be infiltrated by the tumour at the pathology examination. Resection margins had to be free of tumour involvement including lobular carcinoma in situ. Additional eligibility criteria were as follows: patient’s informed consent, a performance status of <1 (ECOG scale), left ventricular ejection fraction (LVEF) within normal limits, white blood cells (WBC) ≥4000/mm³, absolute neutrophil count ≥2000/mm³, platelets (PTL) ≥100 000/mm³, total bilirubin <1.2 mg/dl, serum creatinine <1.5 mg/dl, no distant metastases at the moment of study registration, no history of previous cancer except for in situ carcinoma of the cervix and basal cell skin cancer, no other previous/concomitant diseases interfering with study participation, no previous medical and/or radiation therapy for breast cancer, interval elapsed between date of surgery and date of study randomisation not exceeding 30 days and adequate non-hormonal birth control measures implemented before study registration. The study protocol was reviewed and approved by the ethics committee of each participating institution.

Initial staging consisted of medical history, physical examination, routine haematocohetry survey, bone scan, chest X-ray, liver ultrasound and mammography. The follow-up evaluation consisted of the same work-up performed at the initial staging. The first evaluation was done after the end of chemotherapy, and once a year thereafter. A medical history and physical examination were scheduled once every 3 months for the first 2 years, and once every 6 months thereafter.

Toxicity was graded according to the WHO criteria and evaluated once every 3–4 weeks during chemotherapy treatment. LVEF was assessed by muga scan or echocardiography at baseline, after course 4, course 7 and 12 months after the randomisation date.

Eligible patients were centrally randomised at the operational office of the chemotherapy unit of the Jules Bordet Institute, Brussels, Belgium.

Treatment

CMF was administered for six cycles (i.e. cyclophosphamide 100 mg/m² p.o. on days 1 to 14, methotrexate 40 mg/m² i.v. on days 1 and 8, 5-FU 600 mg/m² i.v. on days 1 and 8; cycles every 28 days). Tamoxifen, 20 mg daily for 5 days, was administered to post-menopausal patients with ER-positive or unknown tumours. Hormonotherapy started after the last cycle of chemotherapy.

Radiotherapy started after the end of chemotherapy. This treatment was mandatory in case of breast-conserving surgery and optional in case of previous mastectomy. In the latter case, before participating in the study, each institution specified the institutional guidelines with regard to eligibility criteria for radiotherapy after mastectomy. These guidelines had to be followed for all patients entered into the study.

Treatment delay was allowed in case of myelosuppression (i.e. WBC <3500/mm³ and/or PLT <100 000/mm³) persisting at the moment of next cycle administration. In case of myelosuppression persisting beyond 2 weeks from the supposed day of re-treatment, a 20% dose reduction was implemented to allow treatment continuation. In case of myelosuppression at day 8 during CMF treatment, a 50% CMF dose reduction was indicated if the WBC count was ≥2500 and <3500/mm³, and/or the PLT count was ≥75 000 and <100 000/mm³. In case of lower WBC and/or PLT counts, CMF day 8 was omitted. A 20% dose reduction was also recommended in cases of grade 3/4 non-haematological toxicity not including alopecia.
Calculation of dose intensity

The treatment records of patients enrolled in the trial were reviewed. For each patient, the intervals between chemotherapy administrations and the body surface area were collected. The dose of chemotherapy in milligrams per square metre (mg/m²) was independently recorded for cyclophosphamide, methotrexate and 5-FU.

Dose intensity was calculated using the method reported by Hryniuk and Bush [13] and Hryniuk and Levine [14]. In brief, the dose intensity for each drug is defined as the total number of milligrams per square meter and per time unit. It was determined for each given drug throughout the whole chemotherapy treatment for each patient by calculating the following ratio: the numerator is the cumulative received dose and the denominator is the total number of weeks elapsed between day 1 of the first CMF cycle and day 1 of the last CMF cycle in weeks, plus one cycle duration. When less than the planned number of cycles was delivered, the denominator was the number of weeks between the date of first treatment and the date of last treatment, plus one cycle time, plus the theoretical number of weeks that would have been required to deliver the missing cycles (planned number of cycles minus number of cycles actually received). This was done to avoid the situation where the dose intensity could be the same for a patient who received a full treatment (six cycles) and a patient who received, for whatever reason, a shorter treatment (less than six cycles).

In summary, the dose intensity (DI) of classic CMF was calculated by the formula: DI = Total dose received (mg/m²)/(Actual time from the first to the last treatment + theoretical time of non-given cycles + one cycle time), where time is expressed in weeks.

The projected dose intensity for each drug is the total amount of drug, expressed as milligrams per square metre (mg/m²), intended based on the classical CMF protocol divided by the projected time schedule, in weeks, of the entire treatment.

Then, the RDI for each drug in the combination was calculated as the ratio between the delivered DI and the projected DI [15].

For each patient, the RDI for the classical CMF regimen was calculated as the arithmetical mean of the RDI of the three drugs that compose this regimen.

Statistical analysis

For inferential purposes, the relative dose intensity was dichotomised using a threshold of 80%.

We looked at the association between relative dose intensity and a patient’s baseline characteristics using chi-square tests for homogeneity.

The baseline characteristics were categorised as follows: age was dichotomised using 50 years as the threshold. The participating institutions were subdivided into four sub-groups. Subgroups 1, 2 and 3 represent the three individual institutions that had the greatest number of patients entered in this study. Subgroup 4 represents the other 13 institutions participating in this study.

The efficacy analysis was carried out on all eligible patients. Disease-free survival was defined as the interval elapsed between the date of randomisation and the date of documented disease relapse, second primary, death without disease relapse or date of last follow-up. Overall survival was defined as the interval elapsed between the date of randomisation, the date of death due to any reason or date of last follow-up. To evaluate the impact of RDI on DFS and on OS, we used Cox regression models.

We performed non-parametric analyses as well as a multivariate analysis with adjustment for covariates known as prognostic factors. These covariates were as follows: number of positive axillary nodes (1–3 or ≥4), tumour size (T1, T2 or T3), age (≥50 years or <50 years) and type of surgery (mastectomy versus conservative surgery).

Results

Patients characteristics

A total of 804 patients were randomised from March 1988 to December 1996. From these, 272 and 265 patients, respectively, were randomised to the EC and HEC arms. From the 267 patients randomised to receive the classical CMF regimen, 12 patients were considered ineligible for the following reasons: inadequate disease stage (seven cases), inadequate cardiac and bone marrow function (one case), violation of other eligibility criteria (two cases), withdrawal of consent before treatment (two cases). One additional patient was excluded from this analysis because of lack of information regarding the body surface area.

The main patient and tumour characteristics corresponding to the 254 eligible cases are reported in Table 1.

For patients randomised to receive classical CMF, the median follow-up was 58 months (range 5–119). One patient was lost to follow-up. At the time of the present analysis, 78 relapses and 56 deaths have been reported.
Overall, the percentage of patients ending the six cycles of the planned CMF regimen was 90%. The mean RDI achieved in the population of 254 patients was 90% (range 8% to 129%) (Table 2).

The main toxicity reasons leading to early treatment discontinuation were digestive intolerance (six cases) and persistent myelotoxicity (five cases). The incidence of grade 3/4 side effects and its relation to received DI is reported in Table 3.

Association between RDI and patients’ baseline characteristics

The subgroup analysis of patients aged ≥50 years and <50 years showed that 81% and 76% of patients, respectively, received ≥80% of the planned chemotherapy dose intensity (P = 0.33). No statistical difference between these subgroups was found regarding the percentage of patients receiving the planned six cycles of CMF (P = 0.21) (Table 4).

We also analysed the relationship between the relative dose intensity and the different institutions participating in this study. No statistically significant difference was found between the percentage of patients who received a RDI <80% and the participating institution (P = 0.50) (Table 5).

Also, no statistically significant difference was found between the percentage of patients receiving less than six cycles of chemotherapy and the participating institution (P = 0.16) (Table 6).

No statistically significant difference was found between the subgroups of patients receiving <80 or ≥80% of the planned DI in relation to the covariates’ T size (T1, T2 or T3), number of positive axillary lymph nodes (1–3 or ≥4) and type

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**Table 2.** Relative dose intensity (RDI) and number of cycles received in the overall population of patients

| No. of patients analysed (n) | 254 |
| Mean RDI % (range) | 90 (8–129) |

| No. of patients receiving: | |
| ≥80% of planned DI | 199 (78%) |
| ≥50 to <80% of planned DI | 39 (16%) |
| <50% of planned DI | 16 (6%) |
| No. of patients receiving: | |
| 6 cycles | 229 (90%) |
| 4–5 cycles | 8 (3%) |
| ≤3 cycles | 17 (7%) |

**Table 3.** Grade 3 and 4 non-haematological toxicities

<table>
<thead>
<tr>
<th>CMF</th>
<th>Relative dose intensity</th>
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<tbody>
<tr>
<td></td>
<td>≥80% (n = 254)</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
</tr>
<tr>
<td>Alopecia (grade 2)</td>
<td>2</td>
</tr>
</tbody>
</table>

CMF: cyclophosphamide, methotrexate, 5-fluorouracil.

**Table 4.** Relative dose intensity and cumulative doses related to patient’s age

<table>
<thead>
<tr>
<th>Patient age</th>
<th>≥50 (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RDI %</td>
<td>92</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(89–96)</td>
</tr>
<tr>
<td>(Range)</td>
<td>(17–127)</td>
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</tbody>
</table>

| No. of patients receiving: | |
| ≥80% of planned DI | 102 (81%) |
| ≥50 to <80% of planned DI | 20 (16%) |
| <50% of planned DI | 4 (3%) |
| No. of patients receiving: | |
| 6 cycles | 117 (93%) |
| 4–5 cycles | 4 (3%) |
| ≤3 cycles | 5 (4%) |

**Table 5.** Relative dose intensity (RDI) of CMF regimen related to participating institution

<table>
<thead>
<tr>
<th>Institution</th>
<th>No. of patients with RDI &lt;80% (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution 1</td>
<td>23/112 (21)</td>
</tr>
<tr>
<td>Institution 2</td>
<td>9/30 (30)</td>
</tr>
<tr>
<td>Institution 3</td>
<td>6/21 (29)</td>
</tr>
<tr>
<td>Institution 4</td>
<td>17/91 (19)</td>
</tr>
</tbody>
</table>

CMF: cyclophosphamide, methotrexate, 5-fluorouracil.

**Table 6.** Cumulative doses related to participating institution

<table>
<thead>
<tr>
<th>Institution</th>
<th>No. of patients receiving &lt;6 cycles CMF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution 1</td>
<td>10/112 (9)</td>
</tr>
<tr>
<td>Institution 2</td>
<td>6/30 (20)</td>
</tr>
<tr>
<td>Institution 3</td>
<td>3/21 (14)</td>
</tr>
<tr>
<td>Institution 4</td>
<td>6/91 (6)</td>
</tr>
</tbody>
</table>

CMF: cyclophosphamide, methotrexate, 5-fluorouracil.
of surgery (mastectomy versus conservative) \( (P = 0.45, 0.97 \text{ and } 0.19, \text{ respectively}) \).

**DFS and OS in relation to RDI**

Covariates included were number of positive nodes (1–3 or >4), tumour size (T1, T2 or T3), age (≥50 years or <50 years) and type of surgery. Comparison between the subgroups of patients receiving <80 or ≥80% of the planned DI indicated no significant difference in DFS (Figure 1), unadjusted relative risk of relapse 1.01; 95% confidence interval (CI) 0.59 to 1.73; \( P = 0.98 \); adjusted relative risk 0.97; 95% CI 0.56 to 1.67; \( P = 0.91 \) and OS (unadjusted relative risk of death 1.12; 95% CI 0.59 to 2.12; \( P = 0.72 \); adjusted relative risk 1.01; 95% CI 0.53 to 1.94; \( P = 0.97 \)).

**Discussion**

The results of this trial indicate that the use of the classical CMF regimen is feasible in the setting of a multicentric phase III trial. The toxicity encountered was acceptable and did not hamper the administration of an adequate DI in the vast majority of patients. In addition, most of the evaluated patients received the planned six cycles of therapy. There is no suggestion of increased grade 3/4 side effects in the subgroup of patients receiving >80% of the planned DI.

Of interest was the finding that, in our analysis, age was not a prognostic factor for the achievement of a RDI ≥80%. This is in contrast with the Milan retrospective analysis in patients receiving the classical CMF regimen as adjuvant chemotherapy. This study showed that the fraction of patients receiving <75% of the planned DI was higher in the post-menopausal compared with the pre-menopausal group, a finding that was proposed as an explanation for the lack of benefit observed in this trial in post-menopausal patients [6].

One possible reason for the improved RDI achieved in our trial even in patients aged ≥50 years, is that the delivery of full-dose chemotherapy on time has been widely advocated in the adjuvant setting. Nowadays, physicians attempt to maintain a good dose intensity and, consequently, do not reduce doses unless justified by appropriate concomitant medical reasons.

When the Milan trial was performed, no data were available regarding the importance of maintaining the planned dose intensity. In addition, nowadays, it is well recognised that adjuvant chemotherapy is effective in post-menopausal patients, and this can of course act as an incentive to maintain an appropriate DI, also in this particular subgroup of patients [5]. Another possible explanation is that the introduction in the 1990s of the new class of selective antagonists of the type three 5-hydroxytryptamine receptor (5-HT3) [16] may have contributed to the good tolerance to classical CMF observed in our study. This effect of 5HT3 receptor antagonists may be particularly important in patients experiencing nausea and vomiting who are not well controlled with dopamine receptor antagonists (e.g. benzamides), during the 14 days of oral cyclophosphamide intake.

This study has also explored the feasibility of the classical CMF regimen in relation to the centre in which the regimen was delivered. It should be noted that no differences in RDI and treatment duration were reported according to the participating institution. This finding suggests that the classical CMF regimen is feasible in a multicentric setting, which includes academic as well as community hospitals.

Institutions with a low accrual were able to deliver a proper RDI with this regimen. One likely explanation is that most treating physicians are now well acquainted with this regimen.

We did not find a difference in DFS and OS between patients receiving a RDI ≥80% and patients who received an RDI <80%. A cut-off of 80% was chosen because of the well-

**Figure 1.** Disease-free survival stratified by relative dose intensity (<80% or ≥80%).
known experiments performed by Skipper [17] using the transplantable Ridgway osteosarcoma tumour.

In this model, a 20% reduction in the average dose intensity of the two-drug combination L-phenylalanine mustard and cyclophosphamide, caused a 50% reduction in the cure rate. This effect was noted before a significant reduction in the complete remission rate occurred [17].

Although some investigators found a DFS advantage for patients receiving the full DI [18–20], others did not find this correlation [21, 22]. This is not completely unexpected because conclusions based on retrospective analyses may be biased. Important patient characteristics may differ in patients who receive and those who do not receive an appropriate DI. In addition, because of the lack of a standard cut-off limit of a ‘good’ RDI, most of these studies used different RDI ranges to define their subgroups [23].

In conclusion, classical CMF was a feasible regimen in the context of a multicentric trial in which academic institutions as well as community hospitals participated. No substantial differences in RDI and cumulative doses were found in relation to patient’s age and participating institution.

References