Dose-intensive weekly cyclophosphamide, methotrexate, 5-fluorouracil, vincristine and prednisolone (CMFP) in advanced breast cancer

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**Summary**  Weekly chemotherapy with cyclophosphamide 80 mg m⁻² day⁻¹ p.o. continuously, methotrexate 35 mg m⁻² week⁻¹ i.v., 5-fluorouracil 500 mg m⁻² week⁻¹ i.v., vincristine 1.4 mg m⁻² i.v. every two weeks and prednisolone 20 mg m⁻² day⁻¹ p.o. alone (CMFP) was prospectively studied in 45 patients. The Cooper regimen was included. However, no untreated patients with advanced breast cancer were included. Of 40 evaluable patients, complete response (CR) occurred in one patient, partial response (PR) in no patients. Stable disease in 11 and five were unevaluable for response. The median relapse-free survival was 25 weeks and median survival for all patients was 31 weeks. The mean dose intensity relative to the Cooper regimen fell from 1.02 to 0.6 within the first 4 weeks of treatment and the median dose intensity achieved for all patients on study was only 0.52. Eighty-seven percent of patients had treatment delays with a mean of 3.9 delays per patient and 71% had dose reductions. Neutropenia was the major toxicity with WHO grade 3 or 4 neutropenia (<1.0 x 10⁹ l⁻¹) in 62% of patients and three septic deaths while neutropenic. Dose-intensive weekly CMFP in this scheme cannot be delivered to previously untreated patients with advanced breast cancer.

Chemotherapy for advanced breast cancer using the combination cyclophosphamide, methotrexate, 5-fluorouracil ± prednisolone CMFP(P) given in a conventional intermittent schedule produces objective responses in approximately 50% of patients, with a response duration of 9 months (Smalley et al., 1983; Tormey et al., 1982). More recently attention has been directed towards the dose and schedule of therapy as a method of improving results with CMF in this disease.

The Cooper regimen, which included vincristine (CMFVP) and a weekly schedule, appeared to be well tolerated with high responses in advanced disease and satisfactory results as adjuvant chemotherapy (Cooper, 1969; Cooper et al., 1979). Hryniuk and Bush (1984) have studied the dose intensity of C, M and F in published data by converting each dose of drug to mg m⁻² week⁻¹ and comparing it directly to the Cooper regimen. They have concluded that many reported CMF programmes deliver much less intense chemotherapy than Cooper described and that a dose–response relationship may exist for C, M and F, especially if actual doses delivered are studied. Hryniuk and Bush's review was retrospective and not all published series of CMF(P) include dose delivery data.

To determine the feasibility of delivering a dose-intensive regimen we studied a weekly CMFVP programme in previously untreated patients with advanced breast cancer. This programme was designed to deliver a dose intensity of 1.02 relative to the Cooper regimen.

**Materials and methods**

**Patients**

Patients presenting to the Peter MacCallum Cancer Institute, Melbourne, Australia, or Auckland Hospital, New Zealand, with advanced metastatic breast cancer which was measurable or evaluable were eligible for this study. Eligible patients had ECOG performance status (PS) 0–3, had not received prior chemotherapy for advanced disease and a minimum of 6 months had elapsed since prior adjuvant chemotherapy. Prior, but not concurrent, radiotherapy and endocrine therapy were permitted.

**Treatment plan**

Patients received cyclophosphamide 80 mg m⁻² day⁻¹ p.o. continuously (560 mg m⁻² week⁻¹), methotrexate 35 mg m⁻² i.v. weekly, 5-fluorouracil 500 mg m⁻² i.v. weekly, vincristine 1.4 mg m⁻² (maximum 2 mg) i.v. every 2 weeks and prednisolone 20 mg m⁻² day⁻¹ p.o. continuously (CMFVP). Prednisolone was used in this dose so that it could be given in equivalent dose intensity to the commonly used daily and 8 intermittent CMFP. One course was defined as four successive weeks of treatment. Patients were seen and treated weekly. Prochlorperazine 12.5 mg i.v. or 25 mg by suppository or metoclopramide 10–20 mg i.v. were routinely given as anti-emetics.

Treatment was continued for at least 24 weeks unless disease progression occurred. Standard WHO response criteria were used (Miller et al., 1981). Relapse-free survival was calculated for complete or partial responders only and measured from the first day of treatment. Time to disease progression was calculated for all patients and measured from the first day of therapy.

All toxicity was prospectively recorded weekly using WHO toxicity criteria (Miller et al., 1981). To assess this programme as an outpatient regimen, treatment was delayed if neutrophils were <1.5 x 10⁹ l⁻¹ (WHO grade 2) or platelets <75 x 10⁹ l⁻¹ (WHO grade 2) or if grade 2 or worse mucositis or other toxicity occurred. Doses of C, M and F were reduced by 25% if sepsis or bleeding occurred with WHO grade 2 toxicity or for WHO grade 3 or 4 toxicity (neutrophils <1.0 x 10⁹ l⁻¹). Vincristine was omitted for severe neuropathy (WHO grade 3 or more).

**Calculation of dose intensity**

Dose intensity was calculated for each patient by converting the total dose of C, M, F and V into the dose received in mg m⁻² week⁻¹. The dose intensities for each drug were then expressed relative to the dose intensities of C, M, F or V in the Cooper regimen (Cooper, 1969; Cooper et al., 1979) (cyclophosphamide 560 mg m⁻² week⁻¹, methotrexate 28 mg m⁻² week⁻¹, 5-fluorouracil 450 mg m⁻² week⁻¹), which was taken as 1.0. The average dose intensity (DI) was then calculated by averaging the DI of each drug and expressing it as a three drug (CMF) or four drug (CMFV) DI. The DI of the starting dose of the weekly programme outlined in the treatment plan was 1.02 relative to Cooper. Prednisolone was not included in the calculation of dose intensity.
Patients who failed to complete one course of treatment (i.e. <4 weekly treatments) had a high calculated dose-intensity but clearly inadequate therapy. These patients were identified separately in our correlation of dose intensity with response. Dose intensity was calculated for each patient weekly. For each patient the profile of any change in dose intensity was determined and the complete dose intensity experience was called the cumulative dose intensity. The average cumulative dose intensity for all patients was calculated and graphed. The log rank test was used to compare survival curves which were generated using the Kaplan–Meier method (Peto et al., 1977).

Results

Patient characteristics

Forty-five patients were treated with weekly CMFVP. The median age of patients was 55 years (range 31–79). On study entry, eight had ECOG PS 0, 14 had PS 1, 13 had PS 2 and 10 had PS 3. Only five patients received prior adjuvant chemotherapy and 37 had prior endocrine treatment. Sixteen patients received no prior radiotherapy and 29 had limited regional radiotherapy only. Only three patients had extensive radiotherapy to >50% of bone marrow areas.

Tumour response

Five patients were invaluable for response, two because of early septic death; two because they received two or less weekly doses and refused further treatment and one ceased therapy after one dose following a perforated peptic ulcer. All 45 patients are included on survival curves in calculations of dose intensity. Of 40 patients evaluable for response, one achieved a CR and 20 PR for an overall response (CR and PR) of 53%, eight had stable disease and 11 progressed on therapy. The median time to disease progression for all patients was 19 weeks, relapse-free survival (for CR + PR) was 25 weeks and median survival was 31 weeks.

Dose delivery

For all 45 patients, 651 weeks on study were documented with 476 weekly treatments received. The first 27 patients (60%) received full dose initially. The subsequent 18 patients started at 0.8 of the initial dose because of poor tolerance in the first 27 patients. No patients started at doses <0.8 of protocol doses. Seventy-one per cent of all patients had dose reductions of CMF on this program. A further 16% of reductions were vincristine alone.

Nine per cent of patients had vincristine related grade 2 or 3 neurotoxicity requiring dose reduction or omission, 5% had vincristine stopped with severe constipation and 2% had vincristine stopped for mild neurotoxicity outside protocol guidelines. Eighty-seven per cent of patients had one or more treatment delays with a mean number of delays per patient of 3.9 (Figure 1). In 47% of patients, treatment was stopped before relapse or progression by the physician because of toxicity and a further 16% stopped because of patient refusal.

Toxicity

The major toxicity encountered was haematological with WHO grade 3 or 4 neutropenia (<1.0 x 10^9/l) in 62 patients (Table 1) and 38% of courses. Neutropenia was the main cause of dose reduction and treatment delay. There were three septic deaths associated with grade 4 neutropenia. Two patients perforated duodenal ulcers, one while on therapy and one patient within one month of completing therapy. WHO grade 2–4 mucositis occurred in 28% of patients. There were few gastrointestinal side-effects with WHO grade 2 or more nausea and vomiting in only 17% of patients.

Dose intensity

The median four drug DI achieved on this study was only 0.52 and three drug DI was 0.53 (Figure 2). The cumulative mean four drug DI dropped from 1.02 at the start of therapy to 0.6 after only four weekly treatments (Figure 3).

Correlation of dose intensity and clinical outcome

The numbers compared are small and no correlation could be detected between four drugs DI and clinical response (Figure 4). Since the median four drug DI was 0.52, patients were divided into two groups with DI <0.52 and >0.52. These groups were well balanced for pre-treatment characteristics such as age and performance status. There were no differences detected in time to disease progression or relapse-free survival for these two groups. The median survival of patients receiving DI >0.52 was 36 weeks and 30 weeks for DI <0.52 (P = 0.8). Similarly, there was no correlation detected between any of these clinical outcomes and three drug DI.

Table 1  Toxicity of patients receiving weekly CMFVP (n = 45)

| WHO grade (%) | 0 | 1 | 2 | 3 | 4 |
|---------------|---|---|---|---|---|
| Haemoglobin   | 27| 33| 24| 11| 2 |
| Neutrophils   | 11| 18| 7 | 38| 24|
| Platelets     | 64| 22| 6 | 0 | 4 |
| Mucositis     | 51| 20| 15| 11| 2 |
| Nausea and vomiting | 42| 40| 15| 2 | 0 |
| Alopecia      | 47| 13| 24| 16| 0 |
| Neurotoxicity | 58| 33| 7 | 2 | 0 |
Conservative and deaths associated with radiotherapy or limited neutropenia to Cooper, (1969).

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