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NADIR NEUTROPHIL COUNTS IN PATIENTS TREATED FOR BREAST CANCER WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE

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ABSTRACT

Objective: **To determine the impact on neutrophils if adriamycin is administered at 60 mg/m² and cyclophosphamide at 600/m² (AC 60/600); and at 50 mg/m² and 500 mg/m² (50/500) in the treatment of breast cancer.**

Design: **Restrospective analysis of nadir neutrophil counts in female mammary carcinoma patients treated with adriamycin/cyclophosphamide combination.**

Setting: **Hurlingham Oncology Clinic, Nairobi and The Nairobi Hospital between March 1995 and August 1999.**

Subjects: **Eighteen patients with breast cancer were treated either for adjuvant purposes or for metastatic disease.**

Intervention: **Chemotherapy with adriamycin and cyclophosphamide at 60/600 or 50/500. Patients were advised to avoid crowded places and given prophylactic broadspectrum antibiotics whenever grade 4 neutropenia occurred at nadir.**

Results: **Grade 3 - 4 neutropenia occurred in 75.5% of treatments at 60/600 and in 56.8% of the treatments at 50/500. Febrile neutropenia followed only one treatment and did not result in death.**

Conclusion: **Neutropenia is frequent and severe at A/C 60/600 and need to be watched out for. Sepsis on the other hand is prevented if meticulous attention is given and corrective measures taken. A/C 50/500 was associated with less occurrences of neutropenia though still very high. Neutropenia should therefore be checked and steps be taken to prevent sepsis even at this dosage.**

INTRODUCTION

Chemotherapy of breast cancer is given for metastatic disease, adjuvant and neoadjuvant purposes. Adjuvant treatment follows surgery for resectable disease while neoadjuvant treatment precedes surgery and is meant to downstage relatively large tumours in order to apply limited surgery. Cyclophosphamide (C) and anthracyclines (Adriamycin [A] and epirubicin [E]) were, before the taxanes, the most active agents in metastatic breast cancer with standard doses resulting in 40-60% overall response rates (1). Anthracycline and cyclophosphamide combinations, with or without 5 fluorouracil (F) [CAF, CEF, CA, CE], in several randomised trials, have produced longer times to progression and occasionally survival than the other chemotherapeutic reference, the CMF [C for cyclosphosphamide, M for methotrexate, F for 5-flourouracil] based combinations(2,3). Cyclophosphamide, adriamycin and 5-fluorouracil (CAF) are given at doses of 400, 40, 400 mg/m^2 respectively; or 500, 50, 500mg/m^2 respectively; or 600, 60, 600mg/m2 respectively.

In experimental biological systems a dose-response curve has frequently been demonstrated with a linear phase that is often steep for tumour tissues(4,5). This is in favour of high dose therapy. CAF 600/60/600 has been clearly demonstrated to be more efficacious than CAF 300/30/300 in the adjuvant setting(6). Addition of 5-fluorouracil to the cyclophosphamide/anthracycline combination does not appear to add much benefit.

MATERIALS AND METHODS

From 1995 we used adriamycin and cyclophosphamide (AC) combination upfront in the treatment of metastatic breast cancer and in the adjuvant setting. Complete blood counts, liver function tests and blood urea and electrolytes were checked routinely at base line and before each treatment. Two-dimensional echocardiography was performed at base line to determine left ventricular ejection fraction (LVEF) in those who had clinical evidence of cardiac abnormality. Patients with inadequate cardiac function were not treated with the anthracycline-based protocol. This test was not repeated if there was no clinical evidence of deterioration in cardiac function. Performance status was also determined using the Karnofsky score at base line. Treatment was not given if the Karnofsky score was less than 30% in the metastatic setting. Patients were not started on treatment until surgical wounds showed signs of healing in the adjuvant setting. Any infections were treated before chemotherapy was started.

The starting doses were 60 mg/m^2 of adriamycin and 600mg/m^2 of cyclophosphamide (60/600) given by slow intravenous push and nadir blood counts were taken at days 10-14 following therapy. Doses were dropped to 50/500 whenever grades 3-4 nadir neutropenia was experienced (WHO scale: grade 3 if neutrophil count 0.5-0.9 x 10^9 /l, grade 4 if neutrophil count <0.5 x 10^9 / litre. If two consecutive treatments at 50/500 were not followed by grade 4 neutropenia then the dose was reverted to 60/600. A total of six courses at three week intervals were given in the adjuvant setting. For metastatic disease, treatment was continued till complete remission or disease progression, or the accepted cumulative dose for the anthracycline (450 - 550mg/m^2) was reached. An analysis of nadir blood counts at AC 60/600 and 50/500 is the subject of this report. Thrombocytopenia occurred, but was only observed after dose-limiting neutropenia and therefore was not considered in this study. Anaemia explained on effects of chemotherapy alone was not experienced in this series.

RESULTS

A total of 18 female patients aged 31 and 62 years were evaluated, (Table 1) with a median age of 41 years. There was no correlation observed between age and the degree of neutropenia. A total of 80 treatment courses were given, 45 at 60/600 and 35 at 50/500, with an average of 4.4 treatment courses per patient. Two patients had prior chemotherapy, three had prior radiotherapy and 13 had none. There was no correlation between prior chemotherapy or radiotherapy and degree of neutropenia in the first AC course at 60/600 (Table 2).

Table 1

Number of cases by age -groups

Age group	No.
30 - 39	2
40 - 49	8
50 - 59	7
60+	1
Total	18

Table 2

Grade of neutropenia in the first course at 60/600, against prior treatment

Grade of neutropenia	Prior treatment: Chemotherapy	Radiotherapy	None	Total
0	0	0	0	0
Grade 1	0	0	1 (100)	1 (100)
Grade 2	1 (20)	0	4 (80)	5 (100)
Grade 3	0	2 (28.6)	5 (71.4)	7 (100)
Grade 4	1 (20)	1 (20)	3 (60)	5 (100)
Total	2 (11.1)	3 (16.7)	13 (72.2)	18 (100)

(radiotherapy/chemotherapy or no prior treatment percentages are in brackets)

Table 3

Grade of neutropenia according to treatment course at 60/600. Number of treatment courses = 45

Treatment course	Grade of neutropenia: 0	1	2 (%)	3 (%)	4 (%)	Total
1	0	0	6 (37.5)	6 (37.5)	4 (29)	16 (100)
2	0	0	3 (25)	5 (41.7)	4 (33.3)	12 (100)
3	0	0	1 (10)	6 (60)	3 (30)	10 (100)
4	0	0	1 (14)	3 (43)	3 (43)	7 (100)
Total	0	0	11 (24.4)	20 (44.4)	14 (13.1)	45 (100)

Table 4

Grade of neutropenia according to treatment course at 50/500 number of treatment courses = 35

Treatment course	Grade of neutropenia: 0	1 (%)	2 (%)	3 (%)	4 (%)	Total
1	0	4 (30.1)	2 (15.3)	3 (23)	4 (30.1)	13 (100)
2	0	3 (27.3)	2 (18.2)	4 (36.4)	2 (18.2)	11 (100)
3	0	0	4 (57)	1 (14.3)	2 (28.6)	7 (100)
4	0	1 (33.3)	1 (33.3)	1 (33.3)	0	3 (100)
5	0	0	1 (100)	0	0	1 (100)
Total	0	8 (22.9)	10 (28.6)	9 (25.7)	8 (22.9)	35 (100)

No pattern of severity emerged for the various courses of treatment (Tables 3-4) at 50/500, but it tended to worsen with increasing courses at 60/600, though this was not significant. The grade of neutropenia was lower at the dosage of 50/500 (Table 4) as compared with 60/600) (Table 3). At 60/600 grade 3-4 neutropenia occurred in 75.5% of the treatments (Table 3) while at 50/500, grade 3-4 neutropenia was experienced in 58.6% of the treatments (Table 4). Febrile neutropenia was only experienced following one treatment and there were no septic deaths.

DISCUSSION

In chemosensitive neoplasms, for a given cytotoxic chemotherapy regimen, dose intensity, dose size and total dose may each have important but different effects on the outcome. Retrospective results from experimental models show that dose intensity is the dominant treatment design variable with respect to the degree of therapeutic response achievable(4-5,7-8). Whereas dose-intensifying cyclophosphamide at conventional doses does not appear to have any therapeutic benefit as demonstrated by Dimitrov *et al*(9) and Fisher *et al*(10), anthracycline dose intensification has been shown to be of benefit(2,3,11,). It therefore makes therapeutic sense to start treatment at the maximum tolerable dose.

The age range for our patients was 31 -62 years with a median of 41 years. There was no correlation between age and degree of neutropenia, findings similar to those

found by Fisher *et al* (12) in an NSABP B- 25 project. NSABP B-25 study also failed to demonstrate therapeutic advantage in dose intensifying cyclophosphamide. Prior chemotherapy or radiotherapy or both, especially if heavy, are expected to predispose to more severe neutropenia because of poor bone marrow stem cell reserves. This did not come out as a problem in our study most likely because of small numbers. For each dosage no pattern of severity emerged for the various courses of treatment, a finding that was also reflected in the NSABP B-25 trial(12).

Neutropenia itself was disturbing in our patients. Grades 3-4 neutropenia experienced in 75.5% of treatments at 60/600, took us by surprise, though it appears comparable to the findings of Jones and colleagues in their placebo arm of CAF 600/60/600(13)

Patients in this arm had grade 3 neutropenia of 88 - 94% between courses 1-4. In the NSABP B-22 trial, WHO grade IV neutropenia occurred in 20.6% of treatments at 60/1200 and in 6.5% at 60/600(10). The corresponding figures in our cases were 31.3% at 60/600 and 16.7% at 50/500. This appears quite divergent. It is not quite clear what racial or environmental factors governing neutrophil response to various chemotherapeutic agents exist. Perhaps prospective studies involving larger patient numbers could be designed to address this issue. No patient in our study went through three consecutive courses at 60/600 without changing over to 50/500. This means that if we had to uniformly apply the more dose intense program, then haematopoietic growth factor support would have to be given routinely. Unfortunately financial constraints do not favour routine use of haematopoietic growth factors, as even workers based in economically more advantaged communities have indicated(14). On the other hand, AC 50/500 could be almost as efficacious as AC 60/600 and could be adhered to except in high-risk adjuvant treatment.

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