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# Nadir platelet counts in African patients on doxorubicin and cyclophosphamide (AC); and cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP).

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## ABSTRACT

AIM The aim of this study was to assess the degree and consequences of chemotherapy-induced thrombocytopaenia in patients on doxorubicin and cyclophosphamide (AC); and cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) in the sub-Saharan Africa setting.

METHODS Breast cancer and non-Hodgkin's lymphoma (NHL) patients placed on AC and CHOP respectively, were followed up at Kenyatta National Hospital, Kenya. Exclusion criteria included HIV positivity and baseline bone marrow involvement. Full blood counts and assessment for haemorrhage were done on at least day one, between days 10-14 and on day 21 of the first two cycles. The primary endpoint for the study was nadir platelet counts. Secondary endpoints were factors associated with the depth of nadir platelet counts and haemorrhage.

RESULTS The median platelet count dropped by 58·7% (167·5 $x10^9$/L) to a nadir of 169 (104-453) $x10^9$/L and by 60·6% (174 $x10^9$/L) to a nadir of 113 (20-360) $x10^9$/L in cycles one and two respectively. Low nadir counts were associated with old age and low baseline platelet counts in both cycles as well as low baseline total lymphocyte counts in cycle one. Higher platelet count drops were associated with higher baseline platelet counts in both cycles and with AC for breast carcinoma in cycle two. Severe thrombocytopaenia occurred only in the second cycle and only in three (3·8%) patients. Only one patient had a minor bleeding episode not attributable to thrombocytopaenia.

CONCLUSION This study suggests that even in the sub-Saharan Africa setting, chemotherapy-induced thrombocytopaenia is insignificant in patients receiving AC and CHOP.

Key Words: Thrombocytopaenia; CHOP protocol; Lymphoma, non-Hodgkin; Breast cancer; developing countries; Cancer.

## INTRODUCTION

Cancer is becoming a serious problem in the developing world. [1-2] Economical and toxicity concerns continue to fuel debate as to whether cytotoxic chemotherapy should be given at all in developing countries. [3-4] In order to uphold the treasured health care values of patient autonomy and dignity, prevention of complications, access, justice, cost control, and equity in provision of care, administration of cytotoxic chemotherapy to patients in developing countries is desirable. [5] Cyclophosphamide, doxorubicin, vincristine and prednisone are relatively cheap cytotoxic regimen drugs which are listed as essential drugs by the World Health Organisation (WHO). Haemorrhage as a result of chemotherapy-induced thrombocytopaenia is among the main toxicity concerns with the administration of cytotoxic chemotherapy; its management and prevention is not without complications, is costly and is a subject of recent as well as ongoing clinical trials.[6-8] Nadir platelet counts provide a measure of the degree of chemotherapy-induced thrombocytopaenia. Although there are indications that chemotherapy-induced thrombocytopaenia may not be as important as chemotherapy-induced neutropaenia in patients with solid tumours and lymphoma, [9-10] its potential occurrence in malignancies which are very common in Africa and are highly chemonsensive such as breast cancer and non-Hodgkin's lymphoma; [9] makes its management a significant issue clinically and economically and therefore a subject worthy of study. For this reason we set out to study the degree of chemotherapy-induced thrombocytopaenia and its relationship to the risk of bleeding in African patients with breast cancer and non-Hodgkin's lymphoma (NHL).

## METHODS

This was a prospective, longitudinal analysis of 78 patients consecutively recruited from the Haematology and Oncology outpatient Clinic, the Cancer Treatment Center, and Medical Wards of Kenyatta National Hospital (KNH) in Nairobi, Kenya during the period of September 2006 to May 2007 after fulfilling the following criteria: aged 13 years and above; histological diagnosis of breast cancer or NHL, staged and eligible for a study chemotherapy protocol, and a written informed consent. For breast cancer cases, the study chemotherapy protocol was three weekly cycles of intravenous Cyclophosphamide *600 mg/m²* day one and Doxorubicin *60 mg/ m²* day one. For NHL cases, study chemotherapy protocol was three weekly cycles of intravenous Cyclophosphamide *750mg/m²* day one, Doxorubicin *50mg/ m²* day one, Vincristine *1·4mg/ m²* day one, and oral Prednisone *60mg/ m²* days one to five. We excluded patients with clinical or biochemical evidence of organ dysfunction not explained by the disease process; an ECOG performance score of three and above; ELISA positivity for HIV Antibody upon routine work up; baseline thrombocytopaenia of less than $100x10^9$/L, or concurrent idiopathic thrombocytopenic purpura. The study was approved by the KNH Research and Ethics Committee.

Full blood count analysis was done for all study patients on day one and between days 10-14 of the first two cycles as well as day 21 of the second cycle. This was done at KNH haematology laboratory using a CELL DYN® 3200 automated haematology analyser (Abbott Diagnostics, Santa Clara CA U.S.A.). The machine platelet counts were double checked with manual platelet counts.

Study patients were evaluated at least on a weekly basis for development of new symptoms and signs, and resolution of those present at commencement of chemotherapy. Significant features which were looked for included the number and severity of episodes of haemarrhage and occurrence of known features associated with haemorrhage in chemotherapy induced thrombocytopaenia[11] which included features of infection such as fever and mucositis. Bleeding episodes were dichotomised into minor episodes (WHO Grades one or two ) or major episodes (WHO Grades three or four).

The primary endpoint was nadir platelet counts. Secondary endpoints included: factors associated with low nadir platelet counts, depths of platelet count fall, and number and severity of bleeding episodes. Descriptive statistics were used for platelet counts and other endpoints. Median nadir platelet counts

and median drops in platelet counts from baseline/ zenith to nadir (median nadir platelet count depths) between and/or within the two cycles were compared using the Wilcoxon signed ranks test for related samples. The relationships between associated factors and median nadir counts as well as median nadir platelet count depths were performed using the Mann-Whitnney U (Wilcoxon Rank Sum W) and Kruskal Wallis tests. Post hoc analysis was done using Tukey HSD test. P value was considered significant at less than .05 for all tests. All data processing and analysis was done using the statistical package SPSS (11.5.1 for Windows; SPSS Inc., Chicago, Illinois, USA).

**Role of the funding source**

The funding source of the study had no role in the design of the study; collection, analysis, or interpretation of the data; or in the writing of this report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

**RESULTS**

A total of 114 patients were screened and 83 patients were recruited of whom 61 (73·5%) had breast cancer and 22 (26·5%) had NHL. Thirty-one patients were excluded for the following reasons: absence of tissue diagnosis (12), recommendation for alternative treatment regimens (three), HIV positivity (14), and withheld consent (two). Five patients were not included in the analysis owing to lost to follow-up (one) and death before day 21 of second cycle (four). Causes of death were mainly oncological emergencies including superior vena cava syndrome, tumour lysis syndrome, and septic shock.

Overall the mean age of patients was 45·2 (SD 12·7) years and median was 44 years with minimum and maximum ages of 14 and 73 years respectively (Table 1). The majority of patients were in the 35-64 year age group. Sixty six patients (84·6%) were female. The female to male ratio was 5·5:1. Among the 61 Breast Cancer patients, one (1·6%) was male; and for the 17 NHL patients 11 (64·7%) were male (M:F ratio 2:1).

The trend in median values for haemoglobin levels and absolute neutrophil counts showed an oscillatory pattern with a median change of about 2g/dL in haemoglobin levels from baseline to nadir and the median haemoglobin nadir levels did not go below 8g/dL which was the institutional trigger for red cell transfusion in patients on chemotherapy. There was on average a $2x10^9$/L drop in median absolute neutrophil count values from baseline values to median nadir counts of below $2x10^9$/L. For total lymphocyte counts there was little change in values.

The median platelet count pattern was oscillatory in the two cycles (Figure 1). The median platelet count dropped by a depth of 167·5 $x10^9$/L in cycle one from a baseline of 336·5 (126-694) $x10^9$/L to a median nadir of 169 (104-453) $x10^9$/L between day one and day 12 then rose by 118 $x10^9$/L to a median zenith count of 287 (125-577) $x10^9$/L by day 22. In cycle two the median platelet count dropped by a depth of 174 $x10^9$/L to a median nadir of 113 (20-360) $x10^9$/L by day 33 then rose by 182·5 $x10^9$/L to a median zenith count of 295·5 (84-628) $x10^9$/L by day 43. This represented 58·7% drop in cycle one and 60·6% drop in cycle two and were both statistically significant drops ($p<0·0005$). The lower median nadir count in cycle two compared to cycle one was statistically significant ($p<0·0005$) but the greater platelet count nadir depth in cycle two (174 $x10^9$/L) compared to cycle 1 (167·5 $x10^9$/L) did not reach statistical significance ($p=0·062$).

By day 12, 58 patients (74·4%) had normal platelet counts and 20 patients (25·6%) had grade 0 thrombocytopaenia. In contrast, by day 33 (Figure 2), 22 patients (28·2%) had normal platelet counts and 27 patients (34·6%) had grade 0 thrombocytopaenia; 18 patients (23·1%) and eight patients (10·3%) had grade one and two thrombocytopaenia respectively; and severe thrombocytopaenia had occurred in three patients (3·8%) - two had grade three thrombocytopaenia (nadir platelet counts of 28·2 x $10^9$/L and 32·3 $x10^9$/L), and one had grade four thrombocytopaenia (platelet nadir count of 20 x $10^9$/L).

The patient with a nadir of 20 x $10^9$/L had stage II NHL and was aged 60, her therapy was interrupted

Table 1: Summary Of Patient Demographic And Clinical Characteristics

| Characteristic | | Overall | | Breast Cancer | | NHL | |
|---|---|---|---|---|---|---|---|
| Sex | Male | 12(15.4%) | 100% | 1(.6%) | 100% | 11(64.7%) | 100% |
| | Female | 66(84.6%) | | 60(98.4%) | | 6(35.3%) | |
| Age (years) | Mean(SD) | 45.2(12.7) | | 46.1(11.1) | | 42.3(17.3) | |
| | Median(Range) | 44(14-73) | | 45(25-73) | | 40(14-67) | |
| Disease Stage | 0 | 1(1%) | 100% | 1(1.6%) | 100% | N/A | 100% |
| | I | 3(4%) | | 3(4.9%) | | 0(0%) | |
| | II | 39(50%) | | 36(59%) | | 3(17.4%) | |
| | III | 18(23%) | | 17(27.9%) | | 1(5.9%) | |
| | IV | 17(22%) | | 4(6.6%) | | 13(76.5%) | |
| ECOG Perfo-mance Score | 0 | 1(1.3%) | 100% | 0 | 100% | 1(5.9%) | 100% |
| | 1 | 66(84.6%) | | 58(95.1%) | | 8(47.1%) | |
| | 2 | 11(14.1%) | | 3(4.9%) | | 8(47.1%) | |
| BSA[$m^{(2)}$] | Mean(SD) | 1.66(0.21) | | 1.65(0.19) | | 1.68(0.28) | |
| | Median(Range) | 1.68(1-2.18) | | 1.68(1-2) | | 1.67(1.13-2.18) | |

NHL, non-Hodgkin lymphoma; SD, standard deviation; ECOG, Eastern cooperative oncology group score; BSA, body surface area.

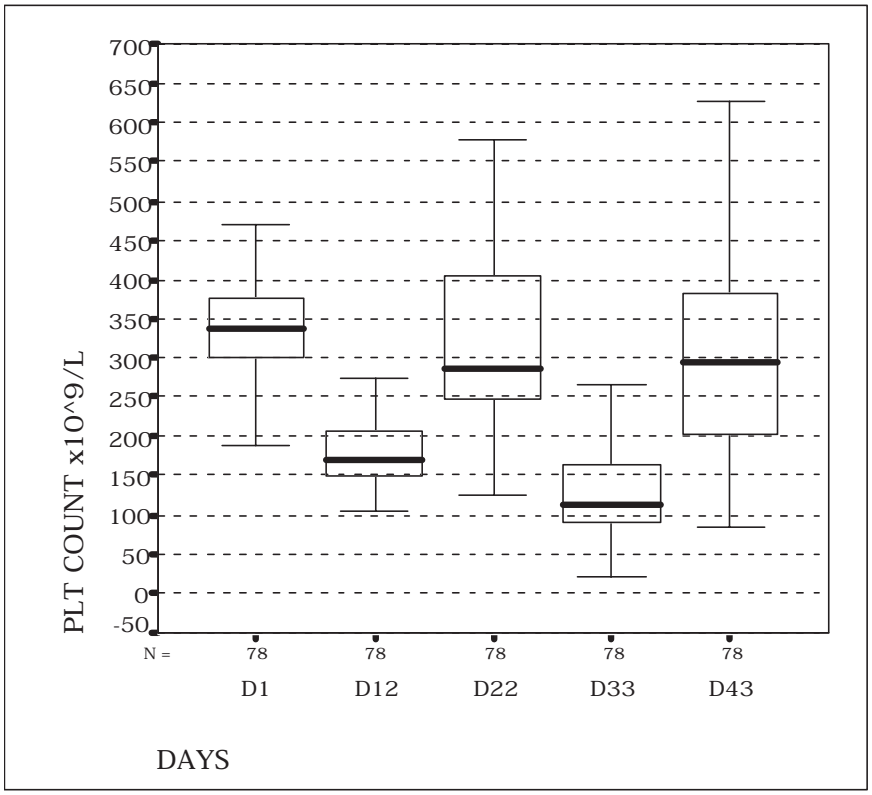


**Figure 1. Boxplot for median platelet counts over the two cycles.** Whiskers represent maximum and minimum values, upper and lower borders of each box represent 75th and 25th percentiles respectively and the middle line in the box represent the median value. D12 represents day 10-14 values in cycle 1 and D33 represents day 10-14 values in cycle 2. D22 and D43 represent day 1 of 2nd and 3rd cycles respectively

twice because of neutropaenia, her baseline platelet (PLT) count in cycle 1 was 141 x$10^9$/L with a baseline absolute neutrophil count of 2·11 x $10^9$/L. The patient with a nadir of 28·2 x $10^9$/L had stage IIIB breast cancer, was aged 66 and had a baseline PLT count of 244x$10^9$/L in cycle one. The third patient who had a nadir of 32·3 x$10^9$/L had stage IIA breast cancer, was aged 56 and had a baseline PLT count of 243 in cycle one. None of these three patients had any episodes of bleeding.

Incidence of thrombocytopaenia was lower compared to neutropaenia in the study in both cycles and thrombocytopaenia was mostly associated with worse grades of neutropaenia (Figure 2).

Low nadir platelet counts were associated with (a) old age (≥60 years) in both cycles, p=0.025 in cycle one and p=0·009 in cycle

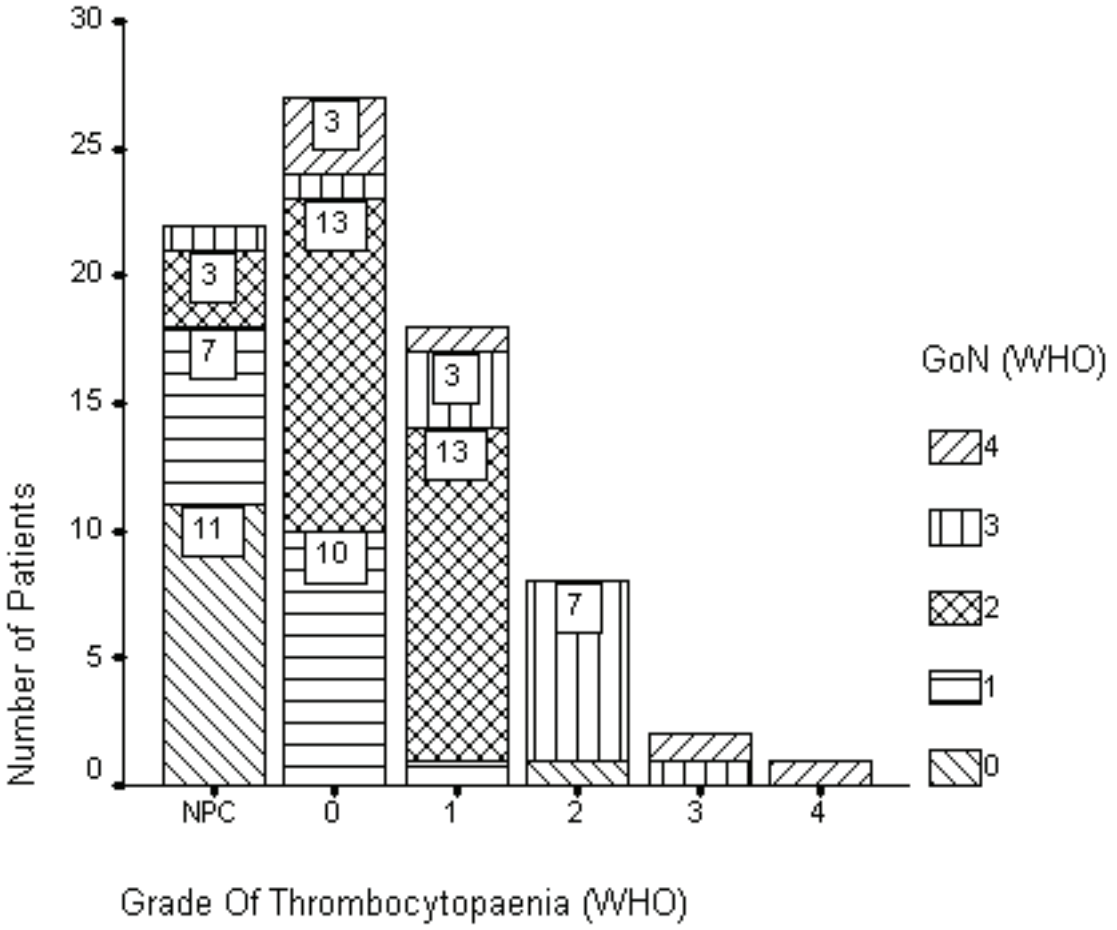


**Figure 2. Nadir thrombocytopaenia and nadir neutropaenia on day 33**. NPC, normal platelet count; GoN, grade of neutropaenia; WHO Criteria*: (a) grade of thrombocytopaenia* - platelet count ($x10^9$/L) ≥100=grade 0; 75-99=grade 1; 50-74=grade 2; 25-49=grade 3 and <25=grade 4. For purposes of this study, grade 0 implies counts ≥100 and <150; counts ≥150 to upper limit of normal were categorized as NPC. Grade 3 and 4 was considered "severe thrombocytopaenia"; (b) *grade of neutropaenia* – neutrophil count ($x10^9$/L) ≥2·0=grade 0; 1·5-1·9=grade 1; 1·0-1·4=grade 2; 0·5-0·9=grade 3; <0·5=grade 4. Unlabelled stacks represent a single patient. This figure shows that severe thrombocytopaenia was associated with equal or worse grades of neutropaenia. Two patients had grade 3 thrombocytopaenia and one patient had grade 4 thrombocytopaenia.

two; (b) low baseline platelet counts in both cycles, p=0·021 cycle one and p=0·029 in cycle two; and (c) low baseline total lymphocyte counts (TLC) in cycle one, p=0·020 (Table 2). Greater platelet count nadir depths were associated with (a) AC therapy for breast cancer in cycle two, p=0·024; and (b) higher baseline platelet (PLT) counts, p<0.0005 in both cycles. Patients in the 14-24 year and 55-64 year age groups had smaller platelet nadir depths in cycle one compared to the rest of the age groups, p=0·011 (Table 3).

Seven patients had higher platelet counts on days 10-14 after chemotherapy than at the beginning of chemotherapy, five of them had an increase in platelet counts in the first cycle and two had an increase in the second cycle. All of the patients, except one, were breast cancer patients on AC. The increases were within the normal range for platelet counts.

One male NHL patient (1·3%) had minor bleeding (grade one; from mucous membranes); with a nadir platelet count of 303 on day 12 and 177 on day 33, an ECOG PS of two, and central nervous system (CNS) involvement for which intrathecal methotrexate was given. This bleeding episode was attributable to methotrexate associated mucositis. Otherwise the rest of the patients reported no bleeding and had no features of bleeding on physical examination. No therapy was interrupted on account of thrombocytopaenia. There were two therapy interruptions both of them owing to neutropaenia of less than 0·5 x $10^9$/L.

Table 2: Factors Related To Platelet Nadir Counts

| Parameters | Category | Cycle 1 | | Cycle 2 | |
|---|---|---|---|---|---|
| | | Median(Range) x$10^9$/L | P Value | Median(Range) x$10^9$/L | P Value |
| Age Groups in Years | >=60 | 147.5(130-205) | ***p=0.025*** | 79.6(20-200) | ***p=009*** |
| | <60 | 169.5(104-453) | | 117(28-360) | |
| Baseline TLC ( x$10^9$/L) | <1.3 | 152(130-255) | ***p=0.020*** | 117(20-346) | p=0.502 |
| | 1.3-1.9 | 170(135-359) | | 106(32-357) | |
| | 2-2.9 | 166(104-421) | | 113(28-360) | |
| | 3-3.5 | 319(163-453) | | 128(59-169) | |
| | >3.5 | 192(169-215) | | 95.4(82-109) | |
| Baseline PLT count (x$10^9$/L) | 100-149 | 138.5(130-170) | ***p=0.021*** | 77(61-154) | ***p=0.029*** |
| | 150-249 | 158.5(133-229) | | 90.6(56-177) | |
| | 250-349 | 161.5(112-359) | | 127(32-346) | |
| | 350-449 | 176(104-421) | | 101.5(20-357) | |
| | >449 | 179(146-453) | | 119.37(56-360) | |

TLC, total lymphocyte count; PLT, platelet. Median nadir platelet counts were used for comparisons because platelet nadir counts in both cycles had a non-normal distribution. This table shows that low nadir counts were associated with (a) old age (≥60) in both cycles, (b) low baseline total lymphocyte count in cycle 1, and (c) low baseline platelet counts in both cycles.

One of these patients was subsequently admitted to the medical ward with febrile gastroenteritis. No study patient received platelet transfusions. One patient received red cell concentrates prior to beginning cycle one on account of a haemoglobin level of 6·49 g/dL, white blood counts (WBC) and PLT counts were normal.

## DISCUSSION

We set out to determine nadir platelet counts for the first two cycles of AC for breast cancer patients and of CHOP for patients with NHL; and to describe factors which are associated with these nadir counts as well as factors which are associated with episodes of haemarrhage. The relatively insignificant effect of the study chemotherapy on haemoglobin level is not unexpected owing to the fact that red blood cells have a long half life (120 days). [12-13] Neutropaenia was common in this study and this is consistent with other studies. [9-10]

Generally our nadir platelet count findings were similar to those of A. Wunderlich et al [11] who showed that firstly, there is an oscillatory pattern to platelet count nadirs in CHOP-21 except that no cumulative effect was demonstrated as is the case in our study; and secondly, there is more pronounced cyclic nadir platelet patterns in elderly patients with lower nadir values. Similarly, JY Blay et al demonstrated that patients with low baseline platelet counts and low baseline total lymphocyte counts were more prone to developing chemotherapy-induced thrombocytopaenia. [14]

Older individuals have been found to be at an increased risk for myelotoxicity because of a reduction in haemopoietic reserve. [15-16] It is logical that low platelet count nadirs should develop in patients who start chemotherapy with low baseline platelet counts. On the other hand the fact that low baseline total lymphocyte counts are associated with low nadir platelet counts may just mean that low baseline total lymphocyte counts act as surrogate markers of a weaker haematopoietic system rather than that they are a direct contributor of low platelet count nadirs. The finding that higher baseline PLT counts were related to greater nadir depths suggests that a fixed proportion (rather than a fixed number) of platelets is affected when patients are given CHOP for NHL and AC for breast cancer such that higher starting PLT count values lead to larger quantities of adversely

Table 3: Factors Related To Platelet Nadir Depths

| Parameters | PLT count nadir depths (cycle 1) | | PLT count nadir depths (cycle 2) | |
|---|---|---|---|---|
| | Median(Range) x109/L | P Value | Median(Range) x$10^9$/L | P Value |
| Age groups (years) | | | | |
| 14-24* | 36 (4-95) | p=0.011 | 63.0(-89 to 436) | p=0.728 |
| 25-34 | 207 (16-341) | | 132.0(85-322) | |
| 35-44 | 183 (-68 to 542) | | 160.0(45-426) | |
| 45-54 | 173 (0-289) | | 156.0(-17 to 393) | |
| 55-64* | 77·5 (-109 to 198) | | 174.0(17-464) | |
| 65-74 | 159 (53-218) | | 159.0(64-467) | |
| Diagnosis/Therapy | | | | |
| NHL/ CHOP | 159 (1-542) | p=0.952 | 113.0(-89 to 467)† | p=0.024 |
| Breast Ca/ AC | 176 (-109 to 339) | | 160.0(-17 to 467)† | |
| Baseline PLT counts (x$10^9$/L) | | | | |
| 100-149 | 7 (-44 to 11) | p<0005 | 60.0(-17 to 64) | p<0005 |
| 150-249 | 47·5 (-34 to 106) | | 149.3(66-174) | |
| 250-349 | 176·5 (-109 to 191) | | 156.0(-89 to 284) | |
| 350-449 | 197 (-1 to 295) | | 313.5(63-403) | |
| >449 | 275 (57-542)‡ | | 392.7(152-467)‡ | |

NHL, non-Hodgkin's lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; AC, doxorubicin, cyclophosphamide; Breast Ca, breast cancer; PLT, platelet; TLC, total lymphocyte count; PLT nadir count depth, drop in PLT count from baseline to nadir values. *Patients in the 14-24 and 55-64 age groups had smaller PLT count nadir depth values compared to patients in the rest of the age groups in cycle 1, †AC therapy for breast cancer had greater PLT count nadir depths than CHOP for NHL in cycle 2; ‡high baseline PLT counts were associated with greater PLT count nadir depths in both cycles.

affected platelets. In terms of thrombopoiesis, larger quantities of platelets would consume larger quantities of thrombopoietin[17-18] leading to low levels of circulating thrombopoietin and therefore a weaker stimulatory effect as platelets suddenly begin to drop, allowing for a deeper drop before the bone marrow is activated enough to restrain the drop. The majority of NHL patients were in the 14-24 and 55-64 year age groups and we demonstrated lower nadir depths in these age groups than the rest of the age groups in cycle one. This was likely because of a mild protective effect against thrombocytopaenia of CHOP in NHL patients, than an effect of age per se. This was clearer in cycle two where breast cancer patients had deeper nadirs than NHL patients. Vincristine and prednisone have been used to treat thrombocytopaenia and their ability to raise platelet counts may moderate CHOP induced thrombocytopaenia compared to AC alone. [19]

The absence of clinically significant episodes of bleeding in the study patients is in keeping with other studies; including the fact that thrombocytopaenia where it occurred, was almost always accompanied by neutropaenia. [9-10] Studies elsewhere (mainly retrospective) have also largely reported low rates of thrombocytopaenia and haemarrhage. [14,20]

The few incidences which occurred in this study of increased platelet counts after chemotherapy could be as a result of secondary or reactive platelet production. [21]

## CONCLUSION

This study suggests that chemotherapy induced thrombocytopaenia does not pose a significant problem in African patients who are put on doxorubicin and cyclophosphamide (AC) and cyclophosphamide, doxorubicin, vincristine & prednisone (CHOP) for breast cancer and NHL respectively. However careful monitoring of platelet count levels should perhaps be done in elderly patients, breast cancer patients and those who start chemotherapy with relatively low platelet count levels; and this would be epitomized by an elderly breast cancer patient with baseline thrombocytopaenia. The study had effectively excluded patients with significant disease bone marrow involvement by excluding patients with platelet counts of less than 100 x$10^9$/L and it also excluded HIV positive patients. Its findings do not apply to these patients.

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## FOOTNOTES

**Contributors**: All authors were responsible for the conception and design of protocol, and approved the final version. YBM collected, assembled, analysed and interpreted the data and wrote the report.

**Conflicts of interest**: The authors declare no competing conflicts of interest.

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