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HAEMATOLOGICAL TOXICITY IN BREAST CANCER PATIENTS ON EPIRUBICIN/CYCLOPHOSPHAMIDE, TAXANE CHEMOTHERAPY AT THE UNIVERSITY COLLEGE HOSPITAL IBADAN, NIGERIA

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ABSTRACT

Background: **Chemotoxicity is a major cause of morbidity amongst breast cancer patients undergoing therapy with haematologic toxicity being the commonest.**

Objective: **To evaluate the haematological toxicities experienced by breast cancer patients on chemotherapy in a tertiary institution in Nigeria**

Design: **A prospective case-control study done over 5 years**

Setting: **Oncological Surgery Division of the University College Hospital Ibadan, Nigeria**

Subjects: **All female breast cancer patients who had at least a total of six courses of chemotherapy as neoadjuvant and/or adjuvant.**

Intervention: **Chemotherapy was administered using the National Comprehensive Cancer Network guideline.**

Main Outcome measures: **Demographical profiles, stage at presentation, histology, serial haemograms. Data collected using a questionnaire screened and entered and analysed using SPSS version 20.**

Results: **Out of the 910 patients reviewed, 218 (24%) patients were included in the analysis. The median age was 44 years. 54% were premenopausal, while 46% were postmenopausal. Of these 83.9% presented with advanced disease. A total of 92 (42%) patients had neoadjuvant chemotherapy, 83 (38.1%) had adjuvant chemotherapy while 43 (19.7%) given palliation treatment. Myelosuppression was the commonest, particularly neutropenia noted in 54(25%) patients, anaemia occurred in 33 (15%) and thrombocytopenia in 1 (0.5%). Febrile neutropenia occurred in 19 patients who required in-hospital care. One (0.5%) patient died from febrile neutropenia. Toxicity occurred**

more towards the latter half of chemotherapy especially with the use of taxanes.

Conclusion: **Taxanes use in these facilities were associated with hematologic toxicity that occurred in the last half of taxanes chemotherapy. Leukopenia with febrile neutropenia most common complication.**

INTRODUCTION

Breast cancer is the most common cancer worldwide and the leading cause of female mortality in low- and medium-income countries (LMIC) (1). In Nigeria more than two-thirds of women with breast cancer present with advanced disease (2-3). The last four decades have witnessed a progressive increase in its incidence worldwide; this time frame has also witnessed a parallel expansion in its clinico-pathologic elucidation and management modalities(4).

Effective management of patients with breast cancer is multimodal and multidiscipline. It involves surgical management, systemic therapy, targeted therapy, hormonal therapy and radiotherapy(5). The introduction of chemotherapy in the twentieth century resulted in improved clinical outcomes in more than a third of patients (6). The earlier combinations included the use of Cyclophosphamide, Methotrexate, 5 Fluorouracil and Vincristine in various combinations with an acceptable result. The advent of the Anthracycline and Taxanes significantly improved disease-free survival. Targeted therapy which evolved along with elucidation of clinico-pathology and tumour biology improved overall survival (6). Overall, systemic therapy is a very important cornerstone in the management of breast cancer worldwide, more so in our setting because of the large number of patients that present with locally advanced and/or metastatic disease(3,5). Chemotherapy toxicity is a major cause of morbidity amongst breast cancer patients undergoing therapy because of the side effect profile of the agent being used. Chemotherapy associated toxicities can manifest acutely or chronically and can affect all organ and systems in the body. Haematologic toxicity from chemotherapy use ranks amongst one of the commonest side effects with reports of up to 40% of patients experiencing it (7). It can manifest as anaemia, leucopenia, thrombocytopenia or any combination of the three which may be life-threatening to the patient. Studies have shown that these toxicities are usually dependent on the dose given and regimen of the medication. Review of most of the cytotoxic agents or combination of agents recommended by the National Comprehensive Cancer Network (NCCN) for treatment of breast cancer revealed that these cytotoxic are myelosuppressive (8). Myelosuppression and its associated complications have been reported to account for most of the morbidities associated with chemotherapy use in patients being treated for breast cancer(9)

This report is aimed at evaluating the haematological toxicities experienced by breast cancer patients on chemotherapy in our institution in Nigeria.

METHODOLOGY

Study Design: The study is a prospective case-control study done over 5 years, i.e. January 2014 till December 2018

Study Population: All female breast cancer patients of the Oncological Unit of the Department of Surgery, University College Hospital Ibadan who had neoadjuvant or adjuvant chemotherapy were prospectively recruited populations.

Study entry criteria: Female patients with histologically diagnosed breast cancer

Data accrual: The patients' demographics, clinical stage at presentation, chemotherapy regimen, results of packed cell volume (PCV), total white cell count (WBC) and platelet count done before the administration of each chemotherapy cycle was recorded. The Eastern Cooperative Oncology Group (ECOG) of each participant at presentation was also recorded. The received dose intensity calculated as standard received dose divided by standard time was also noted.

For this analysis, patients who had completed 6 cycles of epirubicin/ cyclophosphamide to taxanes were included while those who had previous exposure to chemotherapy; major cardiovascular, liver or renal diseases; active infection; inadequate follow-up or pre-existing deranged haematological parameters were excluded. This study was conducted in compliance with the guidelines of the Helsinki declaration on biomedical research in human subjects. Confidentiality of the identity of the patients and personal health information was maintained.

Chemotherapy drug schedules for breast cancer patients in the surgical oncology unit: Following histology diagnosis, staging investigations, and assessment of the patient's cardiovascular status, baseline complete blood assessment is done on the morning of commencement of chemotherapy. Four cycles of the doublet regimen of Epirubicin (100mg/m^2) plus Cyclophosphamide (830mg/m^2) followed by 4 cycles of Docetaxel (80mg/m^2) (EC - D) is given to all patients as advised by the National Comprehensive Cancer Network guideline (10). Some patients had surgery in between the cycles of chemotherapy following partial or complete tumour response to the anthracycline or docetaxel cycle. The patient's hemogram is assessed before each cycle of chemotherapy which is only administered in patients with normal or acceptable hemogram parameters. Premedication with corticosteroids, antihistamines, proton pump inhibitor and anti-emetic agents are administered before the chemotherapy agent. Granulocyte-macrophage colony-stimulating factor (Filgrastim) and antibiotics are used only therapeutically in patients with chemotherapy related neutropenia and sepsis respectively. This regimen is given as neoadjuvant treatment, adjuvant active therapy, a combination of both or adjuvant palliative therapy. Dose reduction, defined as receiving less than 85% of the RDI, chemotherapy dose delay of more than 7 days and early cessation of chemotherapy was noted. Relative dose intensity (RDI) was the proportion received of the reference standard dose for the regimen above (11).

Statistical analysis: All information obtained was recorded in Microsoft Excel spreadsheet. Patients' demography, stage at presentation, histology, baseline hemogram and haemogram at the commencement of each cycle was summarized as percentages, proportions, mean and standard deviation. Statistical analysis was done using SPSS version 20 (Chicago IL USA) and the results were presented in charts and graphs. The relationship between age of participant and clinical stage at presentation with haematological toxicity was analysed using ANOVA while bivariate correlation analysis was done to assess the significance of the change in haematological parameters seen with each cycle of chemotherapy. Statistical significance was set at $P < 0.05$

RESULTS

A total of 910 breast cancer patients were examined and planned for chemotherapy as part of their multimodal treatment in the division between January 2014 and December 2018. Two hundred and eighteen of these had six cycles of EC-T as per protocol with complete medical records. Of

these 218 patients, 2.3% presented with stage I disease, 13.8% at stage II, 65.1% at stage III and 18.8% in stage IV. The median age was 44 years (range 26-69 years) with approximately 4.1 % of patients being over 65 years of age. Slightly over half, 54% were premenopausal, while 46% were postmenopausal. The ECOG performance status was 0-2 in 89% of patients while 3 to 4 in the remaining 11% who had palliative chemotherapy. The predominant histologic type of breast cancer seen was invasive ductal carcinoma which accounted for 93% of cases. The mean body weight and body surface area were 63.8±5.9kg, and 1.4±0.9m^2 respectively. A total of 92 (42%) patients had neo-adjuvant chemotherapy, while 83 (38.1%) had adjuvant chemotherapy with the remaining 43 (19.7%) given as palliative chemotherapy. 1 (0.5%) patient died from febrile neutropenia. Anaemia occurred in 33 (15%) patients with the nadir noted between the 6^{th} and 8^{th} course in 80 % of those developing anaemia. This nadir occurred during administration of taxanes

Dose reduction, delay and RDI less than 85% during the period of administration were 7.3% (16/ 218),1.5% (4/218) and 9.8% (21/218) patients respectively.

Throughout the course of treatment, the mean WBC (x 10^9/L) ranged from 4.90 ± 2.48 to 6.85 ± 3.02, while the mean Absolute Neutrophil Count (x 10^9/L) ranged from 3.54±2.23 to 4.61±2.96. There was mild fluctuation during the entire therapy. Myelosuppression was the commonest, particularly neutropenia was noted in 54(25%) patients with febrile neutropenia occurring in 19 patients who required in-hospital care. The age of the patient and the clinical stage of the disease at presentation had no significant effect ($p > 0.05$) on the haematological profile of the patient following the administration of chemotherapy.

The median duration of admission for management of chemotoxicity was 5 days, ranging from 2 to 20 days. Third generation cephalosporin was the most frequently used intravenous antibiotics in 68.5% of patients with neutropenia. Some 11 patients had varied doses of G-CSF during admission due to severe/febrile neutropenia. Dose reduction and dose delays occurred in 16% and 11% of patients, respectively.

Table-1 shows the clinico-pathologic characteristics of the patients who had chemotherapy. They were aged between 26-69 years with a median of 44 years. Pre-menopausal patients were more than the post-menopausal, while slightly less than two-fifths were ER/PR negative

Table 1

Clinico-pathologic characteristics of patients (n-218)

Characteristics	Value	Percentage
Median Age (Range)	44 years (26-69 years)	
Body Weight (mean) Body Surface Area (mean)	63.8 ± 5.9kg 1.4 ± 0.9m^2	
ECOG		
0 - 2	194	89
3 – 4	24	11
Breast Cancer Stage		
IA	0	0
IB	5	2.3
IIA	8	3.8
IIB	22	10
III	142	65
IV	41	18.8
Histology type		
Invasive Ductal Carcinoma	203	93
Invasive Lobular Carcinoma	13	6
Others	2	1
Immunohistochemistry		
ER +ve	85	38.9
PR +ve	35	16.4
HER2 +ve	20	9
Not done	78	35.7
Intervention drugs category		
Standard	198	91.2
Reduced	16	7.3
Delay	4	1.5
Use of G-CSF	11	5.0
Use of Antibiotics	37	16.9

Table 2

Types of haematological toxicity

Haematological toxicity	Toxicity grade					Total / %
	0	1	2	3	4	
Febrile Neutropenia	3	5	9	2	0	19 / 8.7%
Neutropenia	22	18	14	0	0	54 /24.8%
Leukopenia	0	3	4	4	0	11/ 5%
Anaemia	0	29	4	0	0	33/15.1%
Fever	0	31	32	0	0	63/ 28.9
Allergic reaction/ Hypersensitivity	2	5	0	0	0	7/ 3.2%

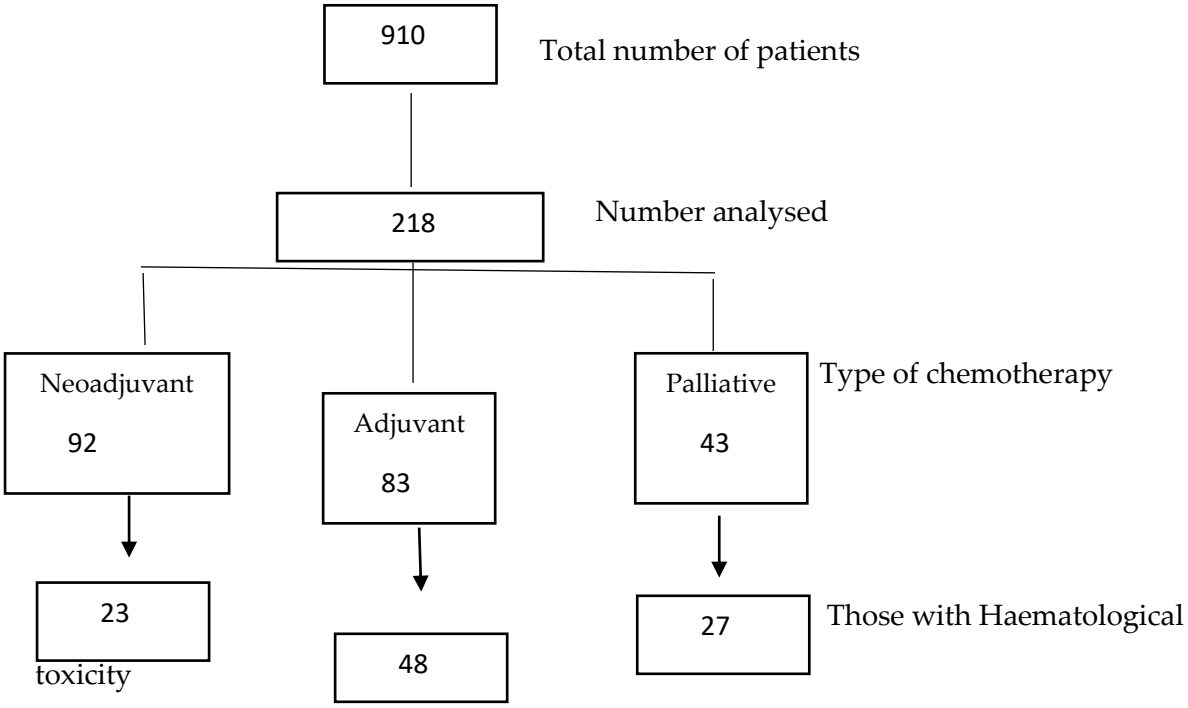

Figure 1: Algorithm of studied analysed patient

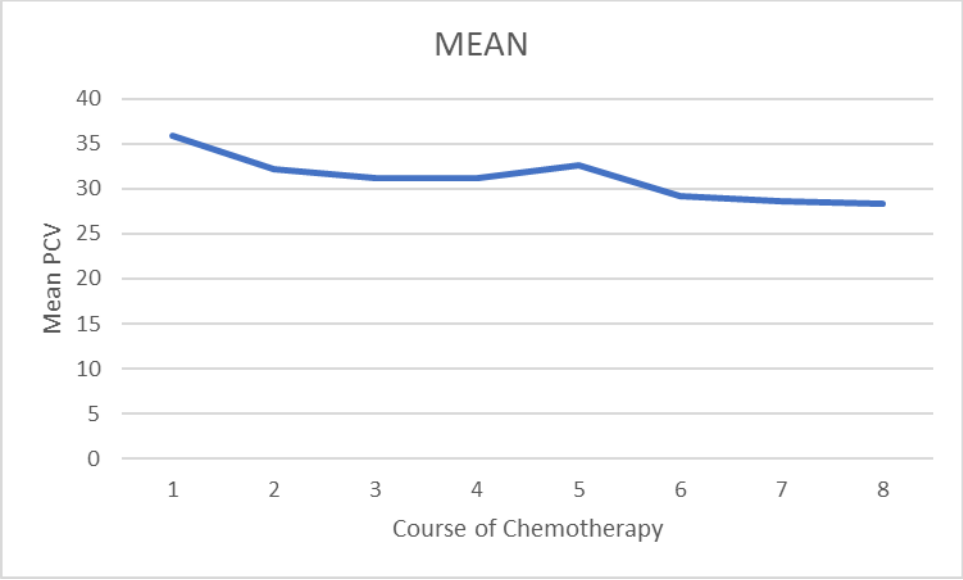

Figure 2: Mean Packed Cell Volume (PCV) during course of chemotherapy

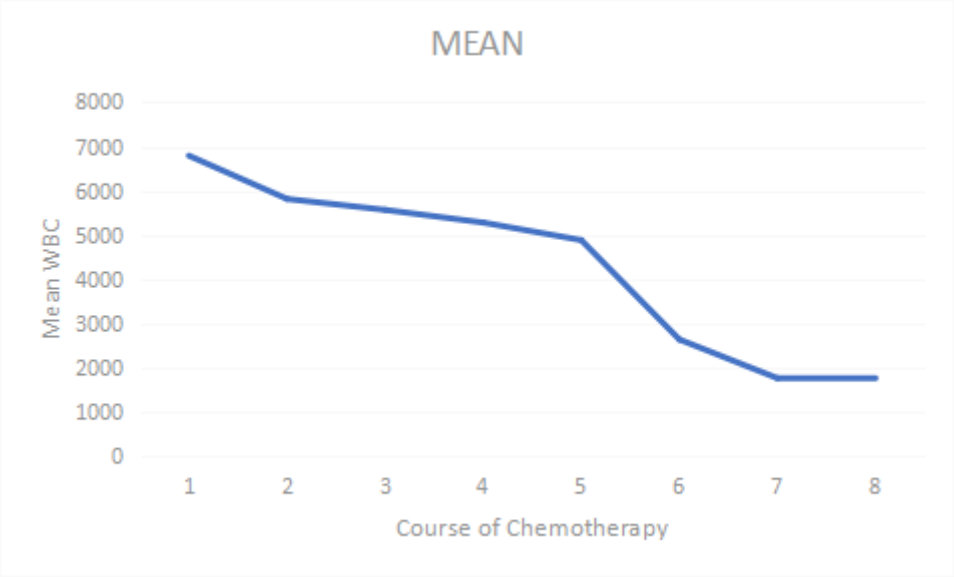

Figure 3: Mean White Blood Cell (WBC) count during course of chemotherapy

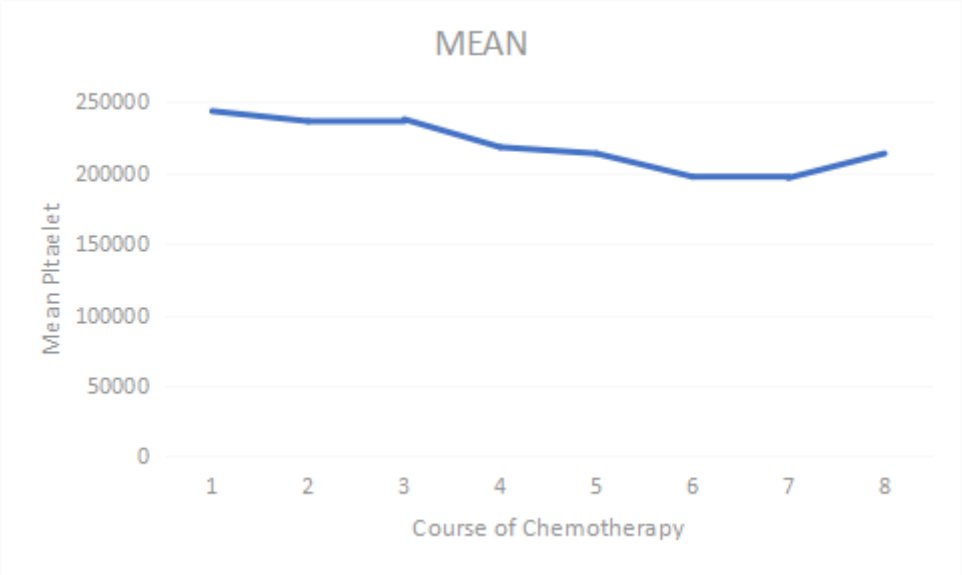

Figure 4: Mean Platelet count during course of chemotherapy

Correlation analysis shows a statistically significant decrease in participants PCV ($p = 0.031$) and WBC ($p = 0.037$) during the 6th cycle of chemotherapy, However, there was no significant reduction in the platelet count of the patients throughout the course of the chemotherapy administration.

DISCUSSION

The aim of chemotherapy use in treatment of cancer entails eradication, prevention of recurrences, palliation and down staging of cancer (12). Its major drawback stems from the inability to identify the difference between malignant cells and rapidly dividing cells (13); thus, leading to its characteristic toxicity that occurs at

therapeutic doses (14). With a seven in ten ratio of late versus early stage breast cancer presentation in our environment (15), most patients in Nigeria require either neoadjuvant or adjuvant chemotherapy at some point during treatment (16).

This narrative fits the often-depicted stereo type of breast cancer in sub-Saharan Africa as being of early onset and aggressive (17). Reasons adduced for the **presentation** with late stage disease are delayed in-hospital presentation, low specialist to patient ratio which are a consequence of the resource constrained nature of health systems in sub-Saharan Africa (18).

The performance index was ECOG 0-2 in two thirds of patients in this study which suggest that background physiology was optimal in majority of cases despite the higher percentage of locally advanced breast cancer (LABC). In the paper by A Watanabe et al (19); ECOG was a predictor of chemotherapy toxicity both on univariate and multivariate analysis. It should be noted that our cohort consist of mostly patients of south western Nigeria origin because of evidence of a variable toxicity potential along continental boundaries due to pharmaco-genetic/ethnic differences in treatment with varied agents exist (20,21). Closely allied to this is the age of the patients. Advanced age is a risk factor for toxicity (22), however our cohort consisted of preponderance of pre-menopausal, middle aged women which may account for the nonsignificant effect age had on toxicity

One third of patients were ECOG ≥ 2 undergoing palliative chemotherapy; this should be approached with caution because, it has been found to offer little benefit on overall survival and has an increased risk of toxicity in them (23). Our results agree with the literature that haematological toxicity is the most common side effect in patients on chemotherapy for breast cancer, with neutropenia ranking highest in our review. Further comparison of the article with our research findings showed that similarities existed in terms of regimen, but G-CSF was used prophylactically in their group. This may explain why the percentage of neutropenia was highest in our cohort when compared to other reports (24,25), that used comparable regimens in a sequential manner. The presence of BRCA-1 gene mutation has been alluded/ linked to the development of early neutropenia in breast cancer patients (24). Excessively higher percentage of neutropenia have been noted to occur in settings where concurrent or concomitant regimens were used or in shorter cycles or schedules (26).

Invariably neutropenia occurred during the Taxanes phase of the sequential AC-T regimen used in this study, with the nadir occurring from the second course of docetaxel. This tallies with the findings by Adrian YS Yip in Hong Kong (27) but is converse to the report by C G Kim et al (28) who had more neutropenia occurring during the AC phase of their patient treatment. We attribute the nadir occurring in the Taxanes phase, to the differences in pharmacokinetics and genetics of doxorubicin/ docetaxel. They have been noted to be different in terms of time to nadir absolute white blood cell and neutrophil count between ethnicities (27). Genetic polymorphism has also been noted to play a crucial part in cyclophosphamide (antimetabolite used as a third drug in the EC-D regimen (29).

About 5% of patients required the use of G-CSF in the therapeutic setting for severe neutropenia complicated by fever (i.e. neutropenia below 1800cmm3 with temperature ≥ 38.0C). Even though this is comparable and within reported range (27), caution should be exercised in comparing regimen due to the varied performance index, stage of disease and number/ duration of chemotherapy.

Other reason adduced by others for evolvement to febrile neutropenia which

were inherent in our cohort include locally advanced breast cancer (26). Clinical guidelines from ASCO and NCCN in the U.S and Europe respectively recommend the prophylactic use of G-CSF, if risk of FN is ≥ 20%; when risk is intermediate 10-20%, consideration should be given to old age, previous chemo radiation, pre-existing neutropenia or infection, performance index and hepatic or renal function (28). From the foregoing, the ideal will be to administer G-CSF prophylactically at all times in our own setting, however "out of pocket health care financing" and its attendant realities dictates otherwise, thus its use in a reactionary or therapeutic manner.

Moderate anaemia was noted from the fifth course of chemotherapy with the nadir being reached by the 7th course. About 15 % of the patients in our cohort had anaemia however all had Grade I to II anaemia. This is to similar studies done by Bajpai J et al and Yip YS (26,30) in which anaemia was a less commonly observed haematological toxicity.

Thrombocytopenia occurred in one patient and this was not statistically significant. It seems that the megakaryocyte cell lines are not as affected as other blood cells by the myelosuppression due to chemotherapy. Several studies assessing haematological toxicity show similar observation (26,31). This observation may be because of the wide margin of the normal range for platelet count which is between 150,000 to 450,000 platelets per microliter of blood (32).

Overall, the rate of dose reduction and delay was lower when compared to other reports (28), Closer analysis show that it was during the docetaxel phase of the chemotherapy regimen that the RDI reduction was noted. We note however that we used the same drug combination and schedule with the latter, while the former used a solitary regimen.

CONCLUSION

Haematological toxicity occurred towards the latter half of chemotherapy regimen especially with the use of Taxanes. leukopenia was the most common complication with febrile neutropenia being the most severe. We recommend strict adherence to the NCCN protocol and its implications be considered based on the treatment setting.

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