Original Article

Chemotherapy-Induced Electrolyte Disorder and Nephrotoxicity in Cancer Patients from Selected Nigerian Tertiary Health Care Hospitals

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Abstract

Background: Chemotherapy is an important treatment modality widely employed for cancer management. The study investigated nephrotoxicity and electrolytes disorders induced by chemotherapy in the cancer patients undergoing chemotherapy in selected Nigerian Tertiary Health care.

Methodology: The participants of the study comprised 130 cancer patients aged 18- 70 years, purposively recruited from three medical centers in south-west Nigeria. Participants' socio-demographics and chemotherapy administered were obtained using questionnaire. Three milliliters of blood sample was collected intravenously from the participants before and after the last course of chemotherapy, and centrifuged at 3000rpm for 10 minutes to obtain serum. The levels of electrolytes, creatinine, and urea in the serum samples were determined spectrophotometrically by automated Roche Hitachi 912 Chemistry Auto-Analyzer. The estimated glomeruli filtration rate (eGFR) was calculated using creatinine based Ukidney online eGFR-calculator while nephrotoxicity was determined according to U.S National Cancer Institute Common Terminology Criteria for Adverse events version 4.0. Collected data were expressed as mean ±standard error of the mean using IBM- SPSS version 22.0software. T- test were employed to test for significance at $P < 0.05$.

Results: Findings from the study revealed significant decrease in the pre-chemotherapy sodium, potassium, chloride ion levels and eGFR as compared to that of post chemotherapy. Also, a significant increase in the pre-chemotherapy creatinine and urea levels as compared to that of post chemotherapy was observed.

Conclusion: Overall, the significant reduction in the electrolyte profiles and estimated eGFR alongside with the significant increase in the mean creatinine and urea profiles recorded after chemotherapy administration confirmed chemotherapy-induced electrolytes disorders and renal toxicity in the cancer participants.

Keywords: Spectrophotometry; Chemotherapy; Nephrotoxicity; Estimated glomeruli filtration rate; Creatinine.

Introduction

Chemotherapy is an important treatment modality for cancer management.[1] As opposed to other cancer treatment like surgery and radiotherapy,

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chemotherapy is a systemic treatment which aid in primary tumour control, prevention of recurrence and prevention of cancer-related symptoms.[2] Despite these benefits, chemotherapy can cause electrolytes disorders which impairs normal body function.[3] This derangement can either occur in form of high or low electrolytes levels. Most electrolyte derangement occur following the effect of some cytotoxic on the nephron which is the functional units of the kidney.[4] Most important chemotherapeutic agents that are nephrotoxic are the platinum-based agents like cisplatin and carboplatin.[5]

Nephrotoxicity & electrolyte disorders accompanying chemotherapy remain serious clinical challenge of cancer treatment.[6] Little attention is paid to these side effects possibly because it may present with no clinical manifestation at the early stage. Failure to detect them early may lead to worse outcome like renal failure which could worsen the chance of survival, negatively impact on the quality of life and increase financial burden on the health care.[7] Monitoring the electrolyte profile and kidney function indices in the course of chemotherapy will be helpful for timely detection and control of electrolyte disorder and nephrotoxicity. Hence, the study was conducted to investigate chemotherapy-induced nephrotoxicity and electrolytes disorders in cancer patients undergoing chemotherapy in selected Nigerian Tertiary Health care institutions, with the research objectives being to determine the status of kidney function indicators before and after chemotherapy.

Materials and Methods

Experimental Design

A prospective study design was employed for the conduction of the study.

Participants

One hundred and thirty (130) chemotherapy naive cancer patients who had been diagnosed of any type of cancer and of age range 18yrs to 70 yrs were purposively recruited from three selected tertiary health care institutions in Nigeria, where they were receiving treatment, namely: University College Hospital Ibadan (UCH), Lagos university teaching hospital (LUTH), Lagos and Federal Medical Centre (FMC) Abeokuta. All the recruited cancer patients satisfied the inclusion and exclusion criteria for selection. Informed consents in form of written documents were collected from all the recruited subjects prior to their participation in the study.

Inclusion criteria

The participants were selected on the basis that they are histologically confirmed cancer patients of age ≥ 18years, they have not received chemotherapy prior to the onset of the study but set to commence first cycle of chemotherapy. In addition, no clinical, radiological or laboratory evidence of renal abnormality as well as Patients receiving no immunosuppressive drugs prior to chemotherapy

Exclusion criteria

Patients with history of radiotherapy, currently on nephrotoxic drugs as well as HIV/AIDS patients currently on anti-retroviral drugs and with apparent multiple organ dysfunction were excluded from the study.

Ethical Approval

The approval of the study was obtained from ethics review committee of the three selected medical centres; UCH, LUTH and FMC with the following ethics committee assigned numbers; UI/EC/19/0161, CMUL/HREC/11/18/464 and FMCA/470/HREC/01/2019/010 respectively. The procedure followed were in line with the ethical standards of the ethical committee of the selected medical centres on human experimentation. Also, consent in form of written documents was obtained from every participant prior to the conduction of the study.

Clinical Data Collection

Social-demographics of the participants were obtained with self-structured questionnaires, while relevant clinical data of the participants including the administered chemotherapeutic regimens were retrieved from their medical reports.

Sample collection and analysis

Three milliliters (3mls) of blood samples were collected intravenously from the cancer subjects at two intervals; before the commencement of chemotherapy and after the last course of their chemotherapy into a set of well labeled sample bottles. The collected blood samples were left

standing for 30 minutes for serum to separate from the whole blood. The separated serum was transferred into another set of sample bottles and stored in a Bio-freezer set at -80 for future analysis.

Serum Electrolyte Analysis

The levels of sodium, potassium, chloride, urea and creatinine in the serum samples were directly quantified by automated Roche Hitachi 912 Chemistry Auto-Analyzer using ion selective electrode method as described by Yadav and Khodke.[8]

Estimation of glomeruli filtration rate (eGFR) at baseline (prior to chemotherapy) and after the completion of chemotherapy (8th cycle) was monitored by modification of diet in renal disease (MDRD) study equation according to Levey *et al.* [9], using creatinine based Ukidney online eGFR-calculator retrieved from https://ukidney.com/nephrology-resources/egfr-calculator.[10]

Estimated glomeruli filtration rate and ratio of serum post-chemotherapy creatinine level to post chemotherapy creatinine level were employed for the assessment of nephrotoxic effects of chemotherapy in the participants. According to the reference from Ukidney eGFR calculator, eGFR < 90 indicates reduced kidney function (https://ukidney.com/nephrology-resources/egfr-calculator). More so, in line with U.S National Cancer Institute Common Terminology Criteria for Adverse events version 4.0, a ratio greater than or equal to 1.5 indicates nephrotoxicity.[11]

Data Analysis

Mean and standard error of the mean of the collected data were computed using IBM- SPSS version 22.0 Chicago IL, USA) software. T-test and one way Analysis of variance (ANOVA) were employed to test for the significance difference between the experimental groups, with the level of significance considered at $P < 0.05$.

Results

Table 1: Frequency and Percentage distribution of participants by cancer types

Cancer types	Frequency	Percentage (%)
Cervical cancer	39	31.5
Breast cancer	49	39.5
Head and Neck cancer	20	16.1
Follicular thyroid cancer	4	3.23
Ocular Malignancy	4	3.23
Colon cancer	1	0.81
Prostate cancer	7	5.65
Total	124	100

Participants of the study were grouped based on the cancer types they had and percentage and frequency distribution of various cancer group were presented in the Table 1 above. From the table, Breast cancer, cervical and Head and neck cancer were the most prevalent cancer types with percentage distribution recorded to be 49%, 39% and 20% of the total participants of the study respectively.

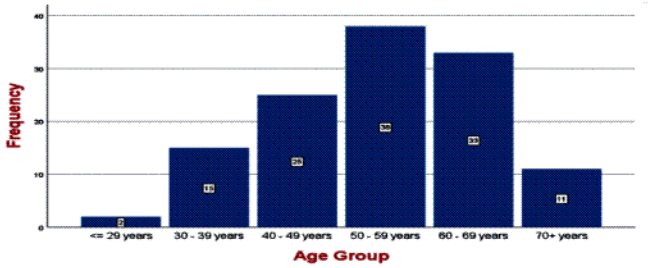

Figure 1: Percentage age distribution of the cancer participants.

The various age groups of cancer patients participated in the study were illustrated in the bar chart in Figure 1 above. From the figure, the age group 50-59, 40-49 and 60-69 years had higher incidence of cancer as compared to other age groups of participants of the study with frequency distribution of 38(%), 33(%) and 25 respectively. However, cancer was most prevalent in age group 50-59 years.

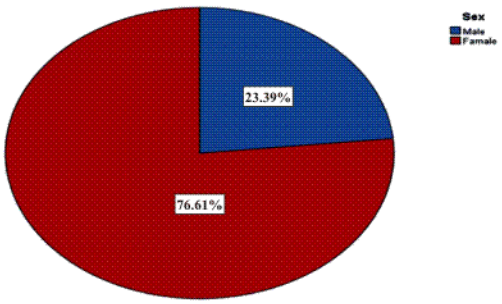

Figure 2: Percentage gender distribution of the cancer participants.

Grouping of cancer participants by gender alongside with their percentage distribution was illustrated with the pie chart in the fig 2 above. From the figure, majority of the cancer participants were female with their percentage distribution (76.61%) more than three times that of male (23.39%).

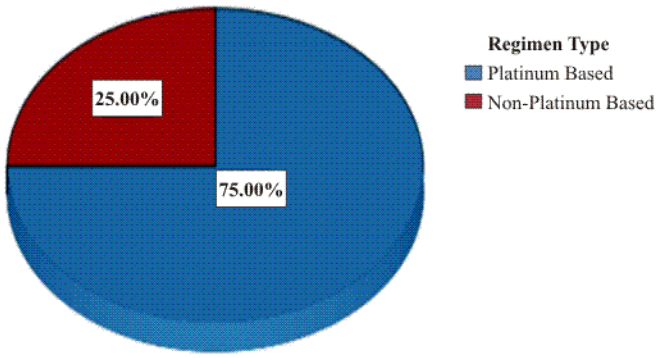

Figure 3: Percentage distribution of participants by administered chemotherapy regimen types.

Participants were placed into platinum and non-platinum based chemotherapeutic regimen groups based on whether chemotherapy received contain platinum or not. Their percentage distribution was presented by the pie chart in the figure 3 above. From the figure, platinum-based chemotherapy was revealed to be the most frequently administered chemotherapy with percentage distribution which is three times (75%) that of non-platinum-based chemotherapy (25%).

Table 2: Serum ElectrolytesUrea and Creatinine Profiles of the participants at pre and post chemotherapy

EUCR/eGFR	Normal Range	Pre-chemo Mean ± SEM	Post-chemo Mean ± SEM	P-value
Na	135- 145(mEq/L)	136.253± 0.382	125.40± 0.474	0.0002*
K	3.5- 5.2(mEq/L)	3.97± 0.045	3.32 ± 0.046	0.0001*
Cl	98-106(mEq/L)	103.47± 1.353	93.15 ± 1.039	0.0019*
HCO_3	21-28 (mEq/L)	23.66 ±0.361	24.69 ± 0.361	0.0056
Urea	7-20(mg/dL)	17.38 ± 1.602	26.88± 2.197	0.002*
CR	0.59- 1.35(mg/dl)	1.09 ± 0.690	1.57 ± 0.346	0.04*
eGFR	≥ 90 (mL/min/1.73m^2)	101.97. ± 6.227	86.17± 3.658	0.0035*

P values with asterisk indicates that the mean values in a column are significantly different (*P <0.05). N.B: Na- sodium; K- potassium; Cl-chloride; HCO_3 -Carbonate ion; CR- creatinine; eGFR- estimated glomeruli filtration rate; EUCR- electrolytes, urea, creatinine; SEM- standard error of the mean.

The EUCR and eGFR profiles of the participants before and after chemotherapy were presented in the table 2 above. From table 2 above, there was a significant decrease (*P < 0.05) in sodium, potassium and chloride ion levels of the participants before chemotherapy as compared to that of post chemotherapy. Contrarily, urea and creatinine levels in the participants at pre-chemotherapy were significantly increased (*P < 0.05) as compared to that of post-chemotherapy. However, a significant decrease in the pre-chemotherapy eGFR values of the participants as compared to that of post chemotherapy was evident from the table 2 above.

Table 3: Post chemotherapy creatinine level and eGFR profile of the participants of different age groups

Participant's Age group	Post-chemo CR Level (mg/dL) Mean ± SEM	Post-chemo eGFR (mL/min/1.732m2) Mean ± SEM
< 50 years	0.927± 0.022	92.8[a]
50-64 years	1.319± 0.063**	80.8[b]
≥ 65years 1.853±0.092*		68.7[c]

*Significant difference (P<0.05) in the values across the column. Values with different alphabets superscript also indicate a significant difference (P<0.05) in the Post chemo eGFR.

The post chemotherapy creatinine level and eGFR profile of the participants of different age group were presented in table 3 above. Age dependent significant (P<0.05) increase and decrease in the post-chemotherapy creatinine levels and eGFR values respectively, were revealed from the table.

Table 4: Post chemotherapy to prechemotherapy mean creatinine ratio of the participants treated with platinum and non-platinum-based chemotherapy regimens.

Postchemo-prechemo mean CR ratio(mCR)	% of participants With Platinum based Regimen	% of participants with Non -platinum based regimen
mCR ≤1.49	(50) 60.2%	(33) 80.5%
mCR ≥1.50	(33) 39.8%	(8) 19.5%
Total	(83)100%	(41)100%

The frequency and percentage of the participants with and without nephrotoxicity induced by chemotherapy participants receiving platinum and non-platinum based chemotherapeutic regimens were presented in the table 4 above. From the table, nephrotoxicity (post-pre chemo CR ratio 1.5 and above) was induced in 39.8% of the participants that received platinum-based regiment. This was more than half of the participants without nephrotoxicity (post-pre chemo CR ratio less than/equal to 1.49) (60.2%). However, for non-platinum chemotherapeutic regimen users, lower percentage (19.5%) of the participants encountered nephrotoxicity as a result of chemotherapy as compared to participants without nephrotoxicity (80.5%).

Discussion

Despite the great revolution brought to cancer treatment by the invention of chemotherapy, plethora of side effects including nephrotoxicity and electrolyte disorders remain its serious clinical challenge. Owing to the indispensable roles of kidney for normal functioning of body system and maintenance of electrolyte homeostasis, determination of its functioning status and electrolyte profiles before each course of chemotherapy will help in timely detection of nephrotoxicity and electrolyte derangement. Hence, the study investigated nephrotoxicity and electrolytes disorders induced by chemotherapy in the cancer patients undergoing chemotherapy in selected Nigerian Tertiary Health care.

Findings from socio-demographics analysis revealed breast cancer, cervical and head and neck cancer as the major cancer types found among the participants of the study with breast and cervical been the most prevalent cancer types among others. This finding is in tandem with that of epidemiological report of Globocan in which Breast cancer and cervical cancer were ranked as first two most frequent cancer in the world respectively.[12]

As regards the distribution of cancer patients by age group, the findings from the study revealed age group 50-59 years to be the group noted with highest cancer incidence, closely followed by age group 60-69. This implies that participants that of middle age were more prone or susceptible to risk of developing cancer. Thus, advanced age is an important risk factor in many cancers' development.[13-14] Therefore, targeting the middle age group for cancer's risk factors awareness and other preventive measures including routine screening for early detection of cancer could mitigate increasing cancer incidence rate.

Moreover, higher cancer incidence was found among the female participants as compared to their male counterparts. This observation from the finding was due to the fact that the commonest cancer in this study (breast and cervix) affect women predominantly. In the same way, differences in the occurrence of various cancer types among male and female gender has been consistently reported from several studies.[15-17]

Furthermore, Majority of the participants in the study received platinum based chemotherapeutic regimen for their cancer treatment as compared to non-platinum-based regimen users as it was evident in the higher frequency and percentage distribution recorded by platinum-based regimen as compared to their counterparts. Platinum based chemotherapeutic regimens are among the most powerful and widely employed for treating numerous solid cancers and it includes popularly known drugs; cisplatin, carboplatin and oxaliplatin, which are commonly use clinically for cancer treatment in every part of the world as well as other recently introduced drugs such as nedaplatin, heptaplatin and cobaplatin that are been used in Japan, South korea and China.[18] The higher potency of platinum-based regimen most especially cisplatin, over other classes of chemotherapeutic regimens as well as their broad spectrum anticancer potential exhibited on solid cancers are the reasons behinds its wide clinical usage.[18] These great features of the drugs stem from their multi mechanisms or mode of action on cancer cells[19] which include binding with genomic or mitochondrial DNA to form DNA lesions or DNA adducts, interfering with processes essential for cell division and proliferation such as transcription, replication and translation, activating several transduction pathways which eventually result to apoptosis or necrosis.[20] Furthermore, Findings from the EUCR and eGFR profile analysis revealed significant decrease ($P<0.05$) in the pre-

chemotherapy electrolyte levels such as sodium, potassium, chloride ion and eGFR values as compared to that of post chemotherapy. This post chemotherapy electrolyte levels reduction is an indication of electrolyte imbalance or disorder accompanying chemotherapy in the studied participants. The reduction in the serum electrolytes levels observed after administration of chemotherapy might be due to their increased renal loss, generally known as electrolyte wasting. Kidney is one of the important systems involved in electrolyte homeostasis. Compromising its functional units by chemical agents will impair important renal related processes including glomeruli filtration which in turn interfere with electrolyte balance.[21]

Electrolyte imbalance is one of the issues faced by cancer patients. It can be associated with ongoing chemotherapy.[3] Manifestation of these chemotherapy-associated electrolyte disorders can lead to multi-organ dysfunction if not corrected promptly.[7] Thus, early recognition and management of these disorders is important in the overall care of the patients with cancer.

In the same line, significant reduction ($P< 0.05$) of pre chemotherapy eGFR values alongside with significant increase in the mean creatinine and urea levels as compared to that of post chemotherapy recorded in the study indicates renal toxicity induced by the chemotherapy. The outcomes of creatinine, urea and estimated glomeruli filtration rate profiles analysis conducted in the study corroborates the findings of the Mburu et al.[25] who reported significant increase ($P< 0.05$) in the creatinine and urea levels before the commencement of chemotherapy as compared to that of after chemotherapy but significant lower ($P<0.05$) estimated glomeruli filtration rate (eGFR) values after receiving the 6^{th} cycles of their post chemotherapy ($P< 0.05$) as compared to that of pretreatment value in the pediatric cancer patients of age range 2-18 years who received chemotherapy at Kenyantta National Hospital, Nairobi, Kenya. Although the participants considered for the study were of different age group and different population with that observed with that of the present study.[22]

Also, comparison of post chemotherapy values of electrolytes, urea, creatinine and eGFR with their respective standard range values revealed that most of the measured kidney function indices except carbonates fall outside the normal standard range. Hence, these discrepancies revealed the incidence of electrolyte derangement and reduced kidney function associated with chemotherapy.

The kidney via nephron plays an indispensable role in many antineoplastic drugs and their metabolites excretion through glomeruli filtration and tubular secretion. However, nephron's functions can be impaired by some cytotoxic drugs, which have potential to exert nephrotoxic effects and eventually resulting in kidney damage.[23] Measurement of glomerular filtration rate, creatinine and urea levels have been widely accepted as important biomarkers of renal function status. A decrease glomerular filtration rate as well as elevated creatinine and urea levels after completion of chemotherapy implies reduced kidney cells functions and clearly revealed renal toxicity caused by the chemotherapy.[24]

However, comparing the degree of nephrotoxicity across platinum based and non-platinum-based chemotherapy regimen users, higher percentage of the participants administered with platinum based chemotherapeutic regimen encountered nephrotoxicity as compared to their non-platinum based regimen counterparts in which only small proportion of the participants experienced nephrotoxic effect, as it was evident from their pre-post chemotherapy creatinine ratio (Table 4). The variation in the frequency of participants that encountered nephrotoxicity observed across both participant groups might be due to the type of chemotherapeutic drugs the participants were administered with as well as different individual participant response to the chemotherapeutic regimen.

Furthermore, observed significant reduction in the eGFR values and significant increase in the creatinine levels of the participants with advancing age group as compared to young age group after administration of chemotherapy reveals advanced age as one of the important patient's related factors that can increase vulnerability to Nephrotoxicity. Since nephrotoxic effects of chemotherapy were more pronounced in participants of advanced age as

compare to young age people, more care and routine monitoring should be done on the elderly patients in the course of chemotherapy for prompt detection and immediate treatment of this side effect of chemotherapy.

Overall, the significant reduction ($P< 0.05$) in the electrolyte profiles and estimated glomeruli filtration rate (eGFR) alongside with the significant increase in the mean creatinine and urea profiles after administration of chemotherapy in the cancer participants confirmed electrolytes disorders and renal toxicity induced by chemotherapy in the cancer participants and this effect was found to be severe with advancing age. Hence, routine monitoring of electrolyte levels and kidney function status in the course of chemotherapy therapy should be embraced by the oncologists as part of preliminary tests to be done before administration of subsequent chemotherapy for their timely detection and treatment, so as improve quality of life and survival of cancer patients.

Conflict Of Interest

The authors declare no conflict of interest.

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