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Chemotherapy-associated renal insufficiency in cancer patients.

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Abstract

Background: Malignancy or its treatment can produce a variety of renal diseasesand renal insufficiency frequently complicates malignancy and its treatment. The aim of this study is to assess the effect of different chemotherapeutic agents on the renal function of patients receiving treatment in a tertiary institution in Nigeria.

Methodology: This is a retrospective study of Glomerular filtration rate assessment among patients who received chemotherapy in Lagos University Teaching Hospital, Lagos, Nigeria from December, 2012 to November, 2013.

Results: 473cases were studied. The mean age was 50± 15.5 years. The peak age range was 4th decade 123(26%). Commom cancers treated were breast cancer (159 cases), cervical cancer (103 cases) and prostate (35 cases). Stages recorded were stage III, 193(40.8%), stage II, 150 (31.7%), stage IV, 115 (24.3%), stage I, 15(3.2%). Treatment modalities revealed that 115(24.2%) had a combination of surgery and chemotherapy, 106 (22.4%) had chemotherapy alone, while 103 (21.8%) had a combination of surgery, chemotherapy and radiation therapy. There was a marked decrease in average GFR from 106.92 at beginning of treatment to 70.49 after completion of chemotherapy. The use of cisplatin showed the highest reduction in the GFR(43 %)after completion of chemotherapy.

Conclusion: Renal Insufficiency is common in cancer patients and drug dosage adjustments might be necessary. Renal function should be evaluated in all cancer patients in a bid to identify patients with a high risk for drug toxicity.

Keywords: *Renal, Insufficiency, Cancer*

Résumé

Contexte: La malignité ou son traitement peut produire une variété de maladies rénales et l'insuffisance rénale complique fréquemment la malignité et son traitement. Le but de cette étude est d'évaluer l'effet de différents agents chimiothérapeutiques sur la fonction rénale des patients recevant un traitement dans un établissement tertiaire au Nigeria.

Méthodologie: Ceci est une étude rétrospective de l'évaluation du taux de filtration glomérulaire parmi les patients qui ont reçu une chimiothérapie à l'Hôpital d'Enseignement Universitaire deLagos, Lagos, au Nigeria de décembre 2012 à novembre 2013.

Résultats: 473 cas ont été étudiés. L'âge moyen était de 50±15,5 ans. La tranche d'âge maximale était la 4ème décennie 123 (26%). Les cancers communs traités étaient le cancer du sein (159 cas), le cancer du col de l'utérus (103 cas) et la prostate (35 cas). Les phasesenregistrées étaient laphase III, 193 (40,8%), phase II, 150 (31,7%), phase IV, 115 (24,3%), phase I, 15 (3,2%). Les modalités de traitement ont révélé que 115 (24,2%) avaientune combinaison de chirurgieet de chimiothérapie, 106 (22,4%) avaientuniquement la chimiothérapie, tandis que 103 (21,8%) avaient une combinaison de chirurgie, de chimiothérapie et de radiothérapie. Il y avait une diminution marquée du TFG moyen de 106,92 au début du traitement à 70,49 après l'achèvement de la chimiothérapie. L'utilisation du cisplatin a montré la plus forte réduction du TFG (43%) après achèvement de la chimiothérapie.

Conclusion: L'insuffisance rénale est fréquente chez les patients atteints du cancer et des ajustements posologiques peuvent être nécessaires. La fonction rénale doit être évaluée chez tous les patients atteints du cancer dans le but d'identifier les patients présentant un risque élevé de toxicité médicamenteuse.

Mots-clés: *Rénale,Insuffisance, Cancer*

Introduction

Malignancy or its treatment can produce a variety of renal diseases. Renal insufficiency frequently complicates malignancy and its treatment. These complications are often preventable or reversible with prompt diagnosis and treatments[1]. Renal insufficiency is a medical condition in which the kidneys fail to adequately filter waste products from

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the blood. Because the mechanisms of renal insufficiency vary significantly in patients with different types of cancer, detection of the disorder is possible only through a careful assessment of the pathophysiologic abnormalities, symptoms and antineoplastic therapy involved in each case [2]. Several antineoplastic agents are potentially nephrotoxic; previous renal impairment as well as combinations with other nephrotoxic drugs may increase the risk of nephrotoxicity during administration of chemotherapy. A few antineoplastic drugs with clearly established nephrotoxicity include: methotrexate which most frequently occurs with high-dose therapy and can be avoided by forced alkaline diuresis and administration of folic acid, streptozotocin but toxicity is prevented by drug discontinuance. Mitomycin-associated renal failure and cisplatin nephrotoxicity is clearly dose-related and used to be considered dose limiting. Renal insufficiency can be prevented by hydration and forced diuresis and thus circumvent the dose-limiting effect of cisplatin-induced renal toxicity [3-7]. A number of methods for evaluating renal function have been proposed, although they have not been specifically evaluated in patients with cancer. The serum creatinine concentration is an unreliable measure in the evaluation of renal function, owing to the influence of a number of non-renal factors[8]. The determination of 24-hour urine creatinine clearance (Clcr) provides a more accurate estimation of the glomerular filtration rate (GFR) than does the serum creatinine concentration alone, but this test is often inconvenient for patients and can be inaccurate in those who do not have cancer. The Cockcroft-Gault formula [9], which estimates the GFR from serum creatinine concentration, is used to detect the onset of renal insufficiency and has been shown to correlate with the 24-hour urine Clcr test. A commonly used surrogate marker for estimatingcreatinine clearance is the Cockcroft-Gault (CG) formula, which in turn estimates GFR in ml/min.It is named after the scientists who first published the formula [9] and this formula expects weight to be measured in kilograms and creatinine to be measured in mg/dL, as is standard in the United State of America. The resulting value is multiplied by a constant, 0.85, if the patient is female.

AIM

The aim of this study is to assess the effect of different chemotherapeutic agents on the renal function of patients receiving treatment at the Department of Radiation Oncology.

Materials and methods

The study was carried out in the Department of Radiation Oncology, Lagos University Teaching Hospital, Idi-araba, Lagos, Nigeria. A retrospective cross-sectional study which reviewed case notes of patients who received chemotherapyin the department over a period of 12 months from the 1st of December 2012 to 30th of November 2013. A total of 473 case notes of cancer patients were reviewed.

The following data were collected for eachpatient using a data extraction form: sex, age, GFR before commencement of chemotherapy and after completion, tumour site, stage of cancer presentation andante cancer drugs prescribed. All patients received six courses of prescribed chemotherapy drugs. Estimations of renal function were made by calculating the Glomerular Filtration Rate (GFR) using the Cockcroft-Gault formula. GFRindicatesglomerular filtration rate, and Serum Creatinine is measured in mg/dL. The formula, as originally published, the equation should be as this:

$$Cr = \frac{(140 - Age)mass(kg)x0.85(iffemale)}{72xSerumCreatinine(mg/dL)}$$

This formula expects weight to be measured in kilograms and creatinine to be measured in mg/dL, as is standard in the USA. The resulting value is multiplied by a constant, 0.85 if the patient is female. Patients who presented with acute renal failure were excluded. Patients with GFR less than 60ml/min/1.73m2 were also excluded in the study.Data was analyzed using the SPSS version 17.Frequency tables were generated to present results and a $p< 0.05$ at 95% confidence interval was considered as statistically significant. Ethical approval was obtained from Lagos University Teaching Hospital, Lagos,Nigeria.

Results

Four hundred and seventy three cases where studied. The mean age was50 ±15.5 years and the peak age range was 4th decade 123(26%). These are presented in Table 1.

Most (363) patients were females accounting for 76.7% of cases, while110 (23.3 %) cases were males as presented in Table 2.

The commonest type of cancer was Breast cancer with 159 cases, followed by cervical cancer with 103 cases and Squamous cell Carcinoma with 30 cases as presented in Table 3.

Most (193) cancer cases were presented in stage 3 of the disease and this accounted for 40.8% of the case. This is followed by 150 cases of stage 2

(31.7%) and 115 cases of stage 4 (24.3%). These are presented in Table 4.

Table 1: Age distribution

Age group(Years)	Frequency	Percentage
<10	6	1.3
11 – 20	2	0.4
21 – 30	37	7.8
31 – 40	87	18.4
41 – 50	123	26.0
51 – 60	97	20.5
61 – 70	70	14.8
71 – 80	43	9.1
81 – 90	8	1.7
Total	473	100.0

Table 2: Sex distribution

Sex	Frequency	Percentage
Male	110	23.3
Female	363	76.7
Total	473	100.0

Treatment modalities include surgery, chemotherapy and radiotherapy. The combination of surgery and chemotherapy was the commonest treatment modality which accounted for 115 cases (24.2%) followed by Chemotherapy alone, 106 cases (22.4%) and combination of three modalities in 103 cases (21.8%) and as presented in Table 5. One hundred and fifty four (154) patients (32.6%) received combination of Cyclophosphamide/ Adriamycin/5-flurouracil, 80(16.9%) received Cisplatin, 68(14.4%) received Oxaliplatin while 60(12.6%) received Capecitabine and the remaining patients 23.5% received other chemotherapeutic agents as presented in Table 6

Overall effect of chemotherapeutic agents on GFR showed statistical significance. There was a markeddecreaseof 34% from an average GFR of 106.92 to 70.49 after completion of Chemotherapy and a p-value of 0.001. The use of cisplatin showed a marked reduction of 43%in the GFR after completion of chemotherapy followed by the use of a combination of Cyclophosphamide/ Adriamycin/Fluorouracil(37%)and Taxanes (31%).Age and gender did not show any significant relationship with GFR and chemotherapeutic agents as P value were > 0.05. (Table 7)

Table 3: Histologic subtypes

Histologic subtypes	Frequency	Percentage
Brain and spinal cord	4	0.8%
Gliomas	2	
Medulloblastoma	1	
Meningioma	1	
Head and Neck	28	6%
Retinoblastoma	3	
Nasopharyngeal carcinoma	12	
Maxillary antrum carcinoma	5	
Thyroid cancer	4	
Mandibular cancer	1	
Carcinoma of the tongue	3	
Chest region	164	34.7%
Breast	159	
Lungs	5	
Gastrointestinal	26	5.5%
Rectal cancer	5	
Colonic cancer	17	
Carcinoid	1	
Hepatocellular carcinoma	4	
Urinary system	14	3%
Bladder cancer	4	
Renal Cancer	8	
Wilms tumor	2	
Gynecologic cancer	137	29%
Endometrid cancer	13	
Cervical cancer	103	
Ovarian cancer	15	
Vulvar cancer	5	
Leiomyosarcoma	1	
Male genitals	35	7.4%
Prostate	35	
Skin cancers	38	8.0
Baso squamous cancer	1	
Dermatofibrosarcoma	2	
Liposarcoma	2	
Melanoma	3	
Squamous cell carcinoma	30	
Bone tumours	3	0.6%
Osteosarcoma	3	
Blood and lymphatic system	23	5.0%
Lymphomas	14	
Plasmacytoma	1	
Multiple myeloma	2	
Kaposi sarcoma	6	
Total	473	100

Table 4: Stages of cancer diseases

Stage	Frequency	Percentage
1	15	3.2
2	150	31.7
3	193	40.8
4	115	24.3
Total	473	100

Table 5: Cancer Treatment Modalities

Treatment modality	Frequency	Percentage
Chemotherapy	106	22.4
Radiotherapy	50	10.6
Chemotherapy and Radiotherapy	58	12.3
Surgery/Chemotherapy	115	24.2
Surgery/Chemotherapy/ Radiotherapy	103	21.8
Surgery/Radiotherapy	41	8.7
Total	473	100.0

Table 6: Type of administered chemotherapy

Drug name	Frequency	Percentage
Adriamycin	6	1.3
Carboplatin	25	5.3
Cyclophosphamide/Adriamycin/ 5-Fluorouracil	154	32.6
Cisplatin	80	16.9
Cyclophosphamide	14	3.0
Darcabazine	6	1.3
Taxanes(Docetaxel, Paclitaxel)	38	8.0
Gemcitabine	10	2.1
Oxaliplatin	68	14.4
Vincristine/Epirubicin/ Cyclophosphamide	12	2.5
Capecitabine	60	12.6
Total	473	100.0

Discussion

This study was conducted to review the incidence of renal insufficiency in cancer patients who received a variety of chemotherapeutic agents whether as single agents or in combination for their treatment. The Cockcroft gault formula[9]was used to estimate the glomerular filtration rate from serum creatinine. This is a much more convenient way of measuring GFR when compared to the 24-hour urinary creatinine clearance estimation which entailed collection of urine over a 24-hour period [10]

Most of the patients enrolled in this study were female,this could be due to the fact that breast cancer accounted for the highest number of cases, it also correlates with other studies done in Nigeria[11], which showed a higher incidence of malignancies among women. However most previous studies done internationally showed a high preponderance of cancers among male [12-13].

A mean age of 50years was noted in this study and this is in agreement with local studies done in this region on cancer incidence [11] as most cancers present in the mid-40s' but contrasts with most studies done internationally [14].The commonest histopathology seen was breast cancer, this is in line with most studies which showed that breast cancer is the commonest malignancy amongst women [11,15].Most of them presented in the late stages of the disease, previous studies done on pattern of presentation of cancer patients in sub-Saharan Africa showed that most presentation are in late stages [16-17]. Also late presentation may be due to poverty, ignorance, wrong diagnosis and alternative treatment which includes native herbal concoction and visit to prayer houses. This late presentation thereby affects prognosis of diagnosis.Most of the chemotherapeutic agents prescribed caused some degree of renal insufficiency in patients but the most reduction was seen in patients who received cisplatin, this is in agreement with most studies done worldwide [4,6]. Cisplatin is a platinum compound, effective therapy for many carcinomas. Its major adverse effect is nephrotoxicity associated with renal insufficiency, although ototoxicity also occurs[18,19]. Cisplatin injures multiple renal compartments. Nephrotoxicity is generally reversible, but it can be permanent. Cisplatin's mechanism of nephrotoxicity is related to its drug characteristics, its renal handling and the kidney response to the cisplatin molecule. Pre-hydration with intravenous normal saline or hypertonic saline was found to be effective in counteracting the toxic effect. Also the addition of mannitol to induce a forced diuresis was also found useful [20]. The use of chemotherapeutic drugs in combination was also found to be associated with nephrotoxicity in this study. There is therefore need for chemotherapy dose adjustments, whether as single agent or in combination, for patients undergoing cancer management

Conclusion

This study has demonstrated the need for assessment of the renal function prior to administration of chemotherapy drugs in order to prevent nephrotoxicity in patients on chemotherapy. The use of antineoplastic agents like cisplatin is associated with severe renal impairment and precautionary measures should be taken prior to administration and dose adjustments made where necessary.

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