World Journal of Innovative Research (WJIR)
ISSN: 2454-8236, Volume-3, Issue-1, July 2017 Pages 01-06

Impairing Of The Renal Function In Cervical Cancer Cameroonian Women Under Cisplatin-Based Therapy: Implications For The Management

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Abstract **— Many reports outlined adverse effects induced by anti-neoplastic drugs such as cisplatin on renal function even though action mechanism is not yet quite understood. This study aimed at evaluating the effect of cisplastin-based concurrent chemoradiotherapy on glomerular filtration in cervical cancer women. A hospital-based study was carried out from November 2013 to march 2014. Four milliliter of venous blood was collected at four time points (T_0, T_1, T_2 and T_3) prior to the chemotherapy. Creatininemia and creatinine clearance rate were adequately computed. Questionnaire form was administered for documenting the baseline characteristics of participants. Medical records were carefully scrutinized to collect complementary information. A total of 26 women aged more than 21 years old were included in the study with a mean age of 59.34 ± 9.96 years. A significant decreasing the renal function between T_0 and T_1 (p = 0.0076) was observed although thereafter no longer significant between T_1 and T_2 (p = 0.1947) and between T_2 and T_3 (p = 0.1190). This study revealed a cisplatin related damaging and dose-depending effect on renal function and underscores the need for cisplatin dose related adjustment with respect to renal function in medical practice.**

Index Terms - Cervical cancer, Anti-neoplastic drugs, Nephrotoxicity, aMDRD, Cameroon.

I. INTRODUCTION

Cancer is a singular word that embraces a large number of diseases that can occur in any organ system throughout the animal kingdom. Cancer is a heterogeneous disease resulting from uncontrollable cell division [1]. Even though one cancer is different from another, they have similar characteristics. Indeed, they are not regulated during cell division and can cause metastasis.

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Cervical cancer is one of the most common malignant tumors of the female reproductive tract [2]. This usually have high mortality rates owing to the difficulty to detect these in early stage [3]. About 500 000 new cases are diagnosed each year, of which an estimated 274 000 are fatal [4]. Human Papilloma virus (HPV) is the major cause of gynecologic cancers, especially its variants 16 and 18 that account both for 70% of cervical cancers [1]. With an estimated of 528 000 new cases each year, cervical cancer is the fourth common women cancer in the world [5]. In 2012, It was the fourth most frequent cause of death per cancer of women around the world which accounted for 266 000 death [6]. In developing countries, it represents the main cause of death per cancer in women [7]. The treatment of this cancer depends on its extent as there are precancerous lesions and invasive cancer. In this latter case, the treatment will depend on the stage of the cancer. For patients with stage over IB1 as defined by the international federation of gynecology and obstetrics (FIGO), it is better to do pelvic radiotherapy associated with weekly cisplatin chemotherapy and curietherapy [8].

However, anti-neoplastic drugs used for cancer treatment exhibit variable renal tolerance profiles. Nephrotoxicity is an inherent adverse effect of certain anticancer drugs. Antineoplasic drugs have a narrow therapeutic index and the amount of drug needed for producing a significant reduction in tumor burden usually elicit an obvious nephrotoxicity [9]. For the treatment of cervical cancer, cisplatin is one of the antineoplasic drugs used for. To eliminate cancer cells, cisplatin binds to DNA, leading to the formation of inter- and intrastrand cross-links. These result in defective DNA templates and the interruption of DNA synthesis and replication. In fast-dividing cells, such as those in cancer disease, cross-linking can further induce DNA damage. Mildly damaged DNA can be repaired, whereas extended damage in cell DNA leads to irreversible injury and cell death [10].

DNA-damaging agents usually have less toxicity in non proliferating cells despite paradoxically the quiescent proximal tubule cells are selectively damaged by cisplatin. The mechanism for this renal cell injury has been the focus of intense investigation for many years, and recent studies suggest that inflammation, oxidative stress injury, and apoptosis probably explain a part of this injury [11]. There is no evidence of tubular reabsorption despite nephrotoxicity in the kidney is the major side effect of cisplatin treatment [12]. So, it looks very crucial to follow patient's renal function

when under cisplastin based treatment despite the elusiveness of knowledge on its action mechanism.

In Cameroon, statistics on cancer are cause of concern. Specifically, cervical cancer is responsible for an age-adjusted incidence and mortality rates of 24 and 19 in 100,000 persons/year respectively [13]. Epidemiological studies on cancer are increasingly growing in the country. Nonetheless, data on the topic still scarce and need continuously for updates. Besides, creatininemia associated with the Cockcroft and Gault formula, in order to determine the glomerular filtration rate (GFR), is the first biological parameter of the follow up of patients under cisplastin-based treatment. Meanwhile, Isnard-Bagnis et al. [9] explained this method had a poor predictive value and therefore were useless for such a follow up. Recently, Launay-Vacher and colleagues demonstrated that intrinsic characteristics such as age, gender and race were key confounders throughout this follow up [14]. As a result, a new approach based on the modification of diet in renal disease (MDRD) equations was proposed [15].

Thus, this study aimed at evaluating the effect of cisplastin-based concurrent chemotherapy on glomerular filtration, using MDRD equations based method, in cancer women. To our knowledge, no study addressing this question was previously carried out in our country. Finally, the findings in this study will provide basic epidemiological data and help in enhancing the management of cancer patients.

II. MATERIAL AND METHODS

A. *Study site*

The study took place at the Douala General hospital (Littoral region, Douala, Cameroon). This is health facility categorized as first category among public hospitals over the country and first reference hospital to surroundings sub-division medical centers.

B. *Study population*

A total of 26 women aged 38-75 years attending the Douala general hospital were finally enrolled upon consent from November 2013 to march 2014 in the study. Patients were followed up for one month duration each. Questionnaire form was administered to each participant for documenting socio demographical, anthropometric and clinical data. Weight and height were used to compute the body mass index (BMI) and the surface body (BS) using the Du Bois' formula. Medical records of participants were carefully scrutinized to collect information pertaining to the stage of cancer, type of cervical cancer, human immunodeficiency virus (HIV) status and positive diagnosis for other GFR-related confounder disease such as renal failure.

C. *Inclusion and non inclusion criteria*

Any woman aged 21 old years and above, diagnosed with an untreated invasive cervical squamous cell carcinoma, negative result for HIV infection and willing to participate was included in the study. Besides, these women had to be eligible for cisplatin-based concomitant chemoradiotherapy and have a normal value of creatinine blood level prior to the first round of the treatment. On the other hand, women diagnosed with invasive cancer, having previously underwent a pelvic irradiation or systemic chemotherapy, presenting medical contradiction to the cisplatin and refusing to participate in the study were excluded. Prior to blood collection, the aim and objectives of the study were explained in a language women could better understand (French or English), and their questions were answered. Furthermore an informed consent was obtained from each them.

D. *Treatment and blood collection strategy*

Cisplatin-based chemotherapy was administered with respect to the stage of cancer and coupled with radiotherapy. This therapeutic strategy is used in the Douala General hospital for cervical cancer treatment. Four rounds of radiotherapy are performed a week meanwhile chemotherapy one time between two courses of radiotherapy. Thus the treatment algorithm each week is two radiotherapy rounds, one chemotherapy round and two radiotherapy rounds again. Regarding the radiotherapy, participants received 45 gray (Gy) external beam therapy delivered homogeneously to the pelvis 4 days/week in 20 fractions at 2.25 Gy per fraction. Regarding the cisplatin-based chemotherapy, patients received treatment with regard of the standards 40mg/m^2 weekly. A hydration with 1500 mL was performed before the administration of cisplatin. In addition, antiemetic drugs were administrated to fight against vomiting. Seven days after the chemotherapy cisplatin is at its stable phase.

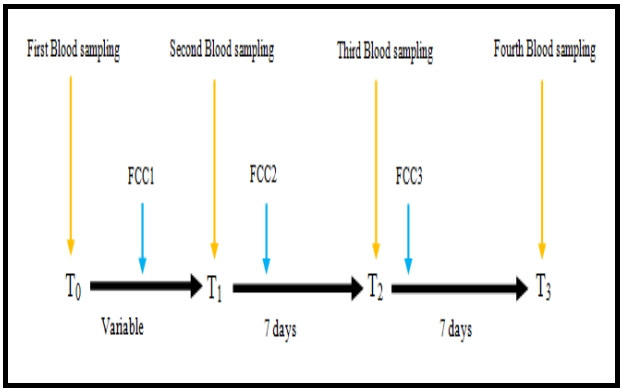

Figure 1: flowchart of the treatment plan and blood sampling

FCC1*: first course of chemotherapy;* ***FCC2****: second course of chemotherapy,* ***FCC3****: third course of chemotherapy*

Blood samples were collected at four time points namely T_0, T_1, T_2 and T_3 as presented in Figure 1. At T_0 women were not supplied with any cancer therapy (radiotherapy and chemotherapy). At T_1 they had already previously received 13.5 Gy and the first course of chemotherapy; at T_2 they had already previously received 22.5 Gy and the second course of chemotherapy. Finally, at T_3 they had already previously received 31.5 Gy and the third course of chemotherapy. The T_0 -T_1 time interval was variable given it was depending on the speed with which the first round of the treatment was initiated in women. As to T_1 –T_2 and T_2 –T_3 time intervals a 7 days delay was scrupulously respected.

E. Blood collection and laboratory procedures

Four milliliter (4 mL) of venous blood were collected and centrifuged at 3500 rpm for 5 minutes and serum obtained was stored at 20°C until creatinine measure. This was measured using the Jaffé kinetic method as previously used. Then, the GFR was determined using the aMDRD formula as follows:

$$GFR = 186 \times C_{creat}^{-1.154} \times age^{-0.203} \times 0.742^{*} \times 1.212^{**}$$

GRF is expressed as mL/min/1.73m^2,
C$_{creat}$ is the creatininemia (mg/dL),
(*****) is the common factor for women
and (******) the common factor for black people.

The normal values of creatininemia range between 50 and 100 µmol/L. Creatinine clearance (Cl_{Creat}) is obtained by multiplying the GFR with the body surface (BS) of the patient. The normal range is 60 mL and above. Below 60 mL, cisplatin dose should be reduced and adapted to the patient. All women included in the study had normal renal function prior supplying with any cancer therapy.

F. Ethical considerations

This study The study was carried out according to the guidelines for human experimental models in clinical research as stated by the Cameroon Ministry of Public Health. Informed consent was obtained from all women and the study was approved by the Ethical Committee of Douala General hospital. Furthermore, participation in the study was strictly voluntary and women were free to decline answering any question or totally withdraw if they so wished at any time.

G. Statistical analysis

All data were verified for consistency, coded, and keyed in an Excel sheet. Then, statistical analyses were performed with SPPS 16.0 for Windows (SPSS, Chicago, IL, USA). Data were presented in table as proportion with confidence interval 95% (95%CI) or mean ± standard deviation (SD) for qualitative and quantitative variables respectively where appropriated. Sample-paired t student test was performed to compare mean values of GFR respectively for the T_0 -T_1, T_1 –T_2 and T_2 –T_3 couples. McNemar's test was used to compare correlated proportion in the marginals of a 2 x 2 contingency tables. Statistical significance was set at $P < 0.05$.

III. RESULTS

A. Baseline characteristics of women

A total of 36 women were enrolled for the needs of the study. Unfortunately, seven of them were excluded owing to their wish to withdraw from the study within the blood collection step and three had creatininemia above the normal range. Thus, the results presented in this paper are summarized for 26 participants.

Overall, the more than 40 years accounted for 96.2 % of all participants. The mean age of study population was 59.34 ± 9.96 years (Table 1). Body mass index (BMI) was normal in most of participants (42.3%; CI95%: 25.6 – 61.1) with 26.60 ± 7.11 kg/m^2 as mean value.

With respect to the stage of cervical cancer, 6 (23.1 %) women diagnosed with stage II of the disease (Table 1). All cases (100 %) of stage I cancer and stage IV were IB and IVA respectively. Out of all cases of stage II cancer and stage III cancer respectively the half was IIA and IIB (2 cases each) for the latter type and IIIA and IIIB for the former one (3 cases each) (data not showed).

B. Renal function results

The Table 2 depicts the variation of creatinine clearance rate and creatininemia with respect to time points. Regarding the former parameter, proportion of participants with creatinine clearance rate less than 60 mL/min and under cisplatin-based treatment was increasing, from 7.7 % (2/26) at T_0 to 28.6 % (6/21) at T_3, over time. Regarding the latter one, the proportion of patients with a creatininemia more than 100 µmol/L increased from 0 % (0/26) at T_0 to 28.6 % (6/21) at T_3. Thereafter, we compared results from these two methods one another in terms of proportion of women with impaired renal function.

The results are somewhat contradictory between these methods although differences were not found significant at T_0 (0 % versus 7.7 % for creatininemia and creatinine clearance rate respectively; McNemar's test p = 0.25), T_1 (30.8 % versus 34.61 %; p = 0.50), T_2 (34.61 % versus 26.9 %; p = 0.50) and T_3 (28.6 %for both; p = 1) time points.

Besides, we found a statistically significant reduction in the creatinine clearance rate (p = 0.0076) between T_0 (89.446 ± 25.192 mL/min) and T_1 (75.235 ± 26.087 mL/min). Thereafter, this reduction is no longer significant between T_1 and T_2 (71.423 ± 25.741 mL/min) (p = 0.1947) and between T_2 and T_3 (66.167 ± 21.455 mL/min) (p = 0.1190) (Figures 2 and 3). The time trend was inversed for creatininemia where a statistically significant increasing over time is recorded (Figures 2 and 3).

Table 1: Baseline characteristics of the study population

Characteristics	Category	Frequency	Percentage (%)	95% CI
Age (years)	[21 - 30[	0	0.0	0.0 – 12.9
	[30 - 40[	1	3.8	0.68 – 18.9
	[40 - 50[	4	15.4	6.15 – 33.5
	[50 - 60[	9	34.6	19.4 – 53.8
	[60 - 70[	7	27.0	13.7 – 46.1
	[70 - 80[	5	19.2	8.1 – 37.9
Mean age (years ± SD)		59.34 ± 9.96		
Body mass index (BMI) at T_0	Underweight	3	11.5	4.0 – 28.9
	Normal	11	42.3	25.6 – 61.1
	Overweight	4	15.4	6.15 – 33.5
	Obesity	8	30.8	16.5 – 49.9
Mean BMI (Kg/m^2 ± SD)		26.60 ± 7.11		
FIGO	Stage I	3	11.5	4.0 – 28.9
	Stage II	6	23.1	11.0 – 42.1
	Stage III	4	15.4	6.15 – 33.5
	Stage IV	2	7.7	2.1 – 24.1
	Hysterectomised	5	19.2	8.1 – 37.9
	Not documented	6	23.1	11.0 – 42.1

FIGO: International Federation of Gynecology and Obstetrics; SD: standard deviation; 95% CI: confidence interval at 95%

Table 2: Variation of the creatininemia and creatinine clearance rate with respect to time points

		Time points			
Variables	**Categories**	T_0	T_1	T_2	T_3
Creatininemia (µmol/L)	< 50	0	0	0	0
	[50 - 100]	26	18	17	15
	> 100	0	8	9	6
Extreme values		50.0 - 96.1	56.7 - 201.9	63.1 - 252.3	66.2 - 242.0
Creatinine clearance rate(mL/min)	< 15	0	0	0	0
	[15 - 30[	0	0	3	2
	[30 - 60[	2	9	4	4
	[60 - 90[	16	9	14	13
	≥ 90	8	8	5	2
Extreme values		52.3 -148.1	27.0 - 127.2	17.1 - 119.6	18.0 - 96.1

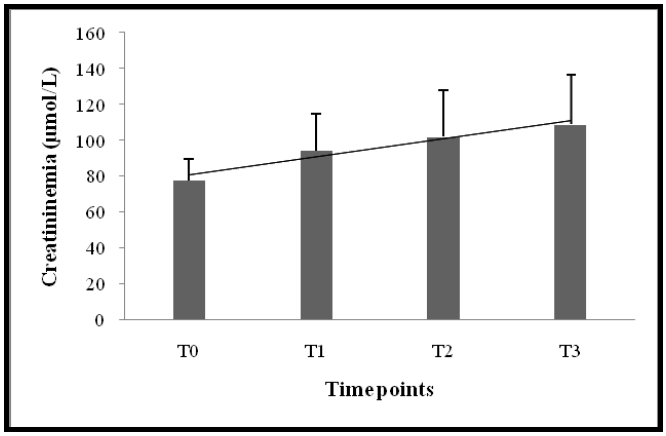

Figure 2: Variation of mean value of creatininemia over time points

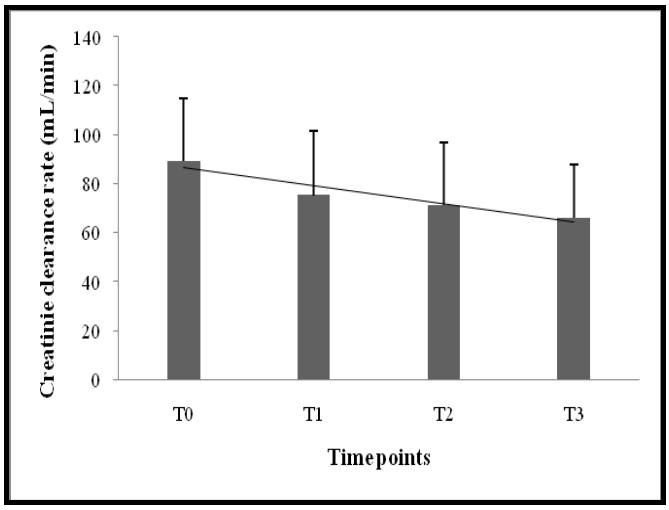

Figure 3: Variation of mean value of creatinine clearance rate over time points

IV. DISCUSSION

Some reports previously underscored anti-neoplastic drugs such as cisplatin elicit obvious nephrotoxicity in people living with a cancer disease. Data on the topic are scarce and not enough investigated in medical practice in Cameroon. This study aimed at evaluating influence of cisplatin-based anti-cancer therapy in women suffering from cervical cancer.

Our study population was old enough with a mean age of 59.34 ± 9.96 years. This result is in line with literature which outlines both incidence, and mortality rates of invasive cervical cancer increases with age, and the bulk of cervical cancer related burden is concentrated in elderly people [16], [17]. This may be explained by the signs and symptoms related long appearance period as well as delayed health seeking behaviour and low level of cancer awareness of this population [18] , [19]. Furthermore, diagnosis of cervical cancer depends mainly on conventional Pap smears and is limited to a few centers for health care in Cameroon such as Douala general hospital. Besides, the diagnosis is not always affordable for most of population in the country whom resources are constrained [20], [21]. As a result, its cost might also represent a challenging problem to deal with in order to mitigate the cancer burden in Cameroon.

This study revealed a cisplatin related damaging and dose-depending effect on renal function. Indeed, we observed a significant impairing the renal function over time since an increasing proportion of women with creatinine clearance rate below 60 mL/min was recorded (from 7.7 % at T_0 to 28.6 % at T_3). In addition, it also observed a dropping the mean values of this biological parameter over time points. This dose-depending nephrotoxicity related to cisplatin treatment was also put in light by many previous reports [22], [23]. Administration of cisplatin for treating the cancer disease increases the risk of acute kidney failure mainly at doses more than 50 mg/m^2 as outlined by [9] and [14]. Although its action mechanism is not yet elucidated, however some authors have suggested inflammation, oxidative stress injury, and apoptosis as possible causes of this impairing the renal function [11]. Thus, these results reinforce the need for further toxicity studies to elucidate the physiological mechanism by which cisplatin injure renal cell as well as adapted administration of cisplatin with respect to creatinine clearance rate during the follow up of patients. In medical practice, the cisplatin dose to be reduced or nullified in patients having creatinine clearance less than 60 mL/min [12]. Moreover, in elderly patients the benefit to risk ratio of cisplatin-based treatment should be strongly evaluated and prohibited when the therapeutic benefice is far much lower than toxicity risk [14]. This fact is questioning since as previously mentioned in this paper most of patients in this study were old enough.

Besides, statistically significant differences, in terms of proportion of patients with impaired renal function, were not found between the methods over time points ($p > 0.05$). However, a few contradictory results between the methods were recorded (data not showed). Thus, agreement was not total between these methods. Isnard-Bagnis et al. [9] have previously pointed out creatininemia based method had a poor predictive value of the renal function since factors such as gender, race and age not taken into account in this method were proved to be key factors in evaluating renal function. Thus, this method is less sensitive and accurate than creatinine clearance based method which deals with these factors [15] and the absence of significance could be explain by the small size of the study sample. As a result, the latter method looks to be more useful in follow up of patients suffering from cancer disease and under cisplatin-based treatment.

A potential limitation of this study is the small sample size. Indeed, this study enrolled 26 women of whom 5 were excluded at T_3 time point. As a consequence, it was unpractical to study the effect of cisplatin-based treatment with respect to confounders on renal function. With the exception of cisplatin, other factors including advanced age, low albumin blood level, stage of cancer, traditional medicines and diseases such diabetes, cirrhosis, ascites or pelvic inflammatory diseases could have interacted and to be responsible for results obtained in this study [14], [23], [24]. Thus, it is needed to design further studies with larger sample size in order to elucidate the interaction game between these aforementioned factors. The resolution of this problem through defining significant diagrams depicting the possible

numerous combination between these factors and their consequence on the renal function might improve the prognosis of this function in cancerous patients under cisplatin-based treatment.

V. CONCLUSION

In conclusion, the results obtained from this study pointed out the deleterious dose related effect of cisplatin-based treatment on renal function over time in women living with cervical cancer. Thus, it would be thoughtful to adapt cisplatin dose with respect to renal function parameter in medical practice. Besides, this requested a more accurate evaluating renal function through aMDRD formula in order to compute the creatinine clearance rate rather using the creatininemia. All this put together will allow preventing any future renal dysfunction such as kidney injury and therefore improve the health and life expectancy of these patients.

ACKNOWLEDGMENT

The authors are deeply grateful to women who participated in this study. Our appreciation also goes to the officials as well as staff of Oncology and radiotherapy units of the General Hospital of Douala for their technical assistance and obtaining administrative clearances .

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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