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Research Article

Prevalence of Gastrointestinal Toxicity in Patients Receiving Platinum-Based Chemotherapy at Douala General Hospital

Prévalence de la Toxicité Gastro-Intestinale chez les Patients Recevant une Chimiothérapie à Base de Platine à l'Hôpital Général de Douala

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ABSTRACT

Background. The purpose of this study was to determine the prevalence of gastrointestinal toxicity in platinum-based chemotherapy and assess factors associated to it in Douala General Hospital. **Methodology.** It was a hospital based descriptive and analytic study carried out in 4 months from January to April 2017. Convenience sampling was used, demographic data and of the occurrence of gastrointestinal toxicity was investigated in patients on any platinum-based chemotherapeutic regimen. **Results:** Out of 100 patients studied, 74% were females and 26% were males with a mean age of 48.9 years. The prevalence of platinum-based chemotherapy induced gastrointestinal toxicity was 91%. The most frequent clinical manifestations were anorexia (79%), nausea/vomiting (73%), taste change (54%), diarrhoea (46%), bloating (23%), constipation (21%), belching (20%) flatulence (20%) and mucositis (18%). Most patients (97.4%) had less than grade 3 toxicity severity for clinical manifestations in general and only nausea/vomiting (1%) and diarrhoea (4%) were life threatening (grade 4 severity). Cisplatin was found to be more emetogenic and to cause more anorexia than the other platins while carboplatin was found to cause more rectal burning. Being at least 40 years old, being on chemotherapy alone compared with concurrent chemoradiation, being on a cisplatinum-based regimen and having received at least 3 cycles of chemotherapy were significantly associated with the occurrence of GI toxicities. **Conclusion.** Gastrointestinal toxicity following platinum-based chemotherapy is very common with many clinical manifestations that can be life threatening. Toxicity is associated to clinical factors. A more in-depth study is recommended.

RÉSUMÉ

Contexte. L'objectif de cette étude était de déterminer la prévalence de la toxicité gastro-intestinale de la chimiothérapie à base de platine et d'évaluer les facteurs qui y sont associés à l'hôpital général de Douala. **Méthodologie.** Il s'agissait d'une étude descriptive et analytique en milieu hospitalier réalisée en 4 mois de janvier à avril 2017. L'échantillonnage de convenance a été utilisé, les données démographiques et de la survenue de la toxicité gastro-intestinale ont été recherchées chez les patients sous tout régime chimiothérapeutique à base de platine. **Résultats :** Sur les 100 patients étudiés, 74% étaient des femmes et 26% des hommes avec un âge moyen de 48,9 ans. La prévalence de la toxicité gastro-intestinale induite par la chimiothérapie à base de platine était de 91 %. Les manifestations cliniques les plus fréquentes étaient l'anorexie (79%), les nausées/vomissements (73%), le changement de goût (54%), la diarrhée (46%), les ballonnements (23%), la constipation (21%), les éructations (20%), les flatulences (20%) et la mucosite (18%). La plupart des patients (97,4 %) ont présenté des manifestations cliniques d'une gravité inférieure au grade 3 et seuls les nausées/vomissements (1 %) et la diarrhée (4 %) ont mis leur vie en danger (gravité de grade 4). Le cisplatine s'est avéré plus émétisant et plus anorexique que les autres platines, tandis que le carboplatine a provoqué davantage de brûlures rectales. Le fait d'être âgé d'au moins 40 ans, d'être sous chimiothérapie seule par rapport à une chimioradiothérapie concomitante, d'être sous un régime à base de cisplatine et d'avoir reçu au moins 3 cycles de chimiothérapie était significativement associé à la survenue de toxicités gastro-intestinales. **Conclusion.** La toxicité gastro-intestinale après une chimiothérapie à base de platine est très fréquente et s'accompagne de nombreuses manifestations cliniques qui peuvent mettre en jeu le pronostic vital. La toxicité est associée à des facteurs cliniques. Une étude plus approfondie est recommandée.

INTRODUCTION

In black Africa, because of the high frequency of cancers diagnosed at locally advanced or metastatic stages, chemotherapy, whether neoadjuvant, adjuvant or palliative, is the first-line treatment for cancers. Just like other treatments, chemotherapy has several side effects. Most cytotoxic drugs used for chemotherapy target rapidly multiplying cells and they act mainly on nucleic acids and their precursors, which are rapidly synthesised during cell division[1]. Currently used chemotherapeutic agents do not make the difference between cancer cells and normal cells undergoing rapid division like bone marrow, gastrointestinal lining, reticuloendothelial system and gonads. Gastrointestinal (GI) toxicity is a common complication of cytotoxic cancer chemotherapy [2]. These symptoms could present as anticipated, immediate or late and are the most common of all the late physical side effects of cancer treatment and have the greatest influence on quality of life [3]. According to Cherwin in a study done in 2012 chemotherapy is known to cause as many as 19 GI symptoms; nevertheless, the most common and well-studied nausea and vomiting. [4,5]. Almost half of the chemotherapy treatment regimens used today contain a platinum drug, such as cisplatin, carboplatin or oxaliplatin alone or in combination with other drugs. However, toxicity associated with these drugs due to their poor specificity is their major disadvantage. Nausea, vomiting, constipation, and diarrhoea, oral mucositis are common GI side effects associated with platinum-based chemotherapy which are debilitating to patients and account for dose limitations and/or interruption of treatment[6,7]. Considering the high frequency of use of platinum-based chemotherapy in our oncology ward, it was therefore necessary to determine the prevalence of gastrointestinal toxicity in platinum-based chemotherapy and assess factors associated to it.

PATIENTS AND METHODS

Study design and sampling

The study was descriptive and analytic with prospective data collection carried out in General Hospital Douala (GHD) from January to April 2017; and involved cancer patients receiving inpatient or outpatient platinum-based chemotherapy. Consented Participants were recruited by convenience sampling and included patients who had received chemotherapy at least once; those aged 18 years or more and accepted to participate. The study excluded patients with (i) cognitive impairment, (ii) GI comorbidities (gastrointestinal obstruction, active peptic ulcer disease (iii) active infection.

Study procedures

Data was collected using a questionnaire that gathered the following variables: demographic data (age, sex, ethnicity, marital status, occupation); clinical and histological data (TNM classification, primary localisation of cancer, GI clinical manifestations); therapeutic data (chemotherapy regimen and dose, cycle number, and any GI supportive medications). GI clinical manifestations were evaluated during the interview and also by weekly phone call. The protocol has obtained ethical clearance from the institutional ethics committee of the University of Douala.

Data management and Data analysis

WHO (World Health Organization) and CTC (Common Toxicity Criteria) grading systems for severity were used for toxicity classification (The grades ranged from 0 (absent) to IV (life threatening) [8]. Patients' data were classified into age groups with 15 years range and cancers ranked accordingly and by sex. Descriptive statistics were used to summarise the data obtained from the sample and data presented using frequency tables and charts. The chi-squared and Fischer's test were used to assess factors associated to GI toxicity. SPSS version 20 Software and the significance threshold of 0.05**.**

RESULTS

A total of 100 cancer patients receiving treatment with any platinum-based chemotherapeutic regimen participated in the study, among them 80% (n=80) were on chemotherapy alone and 20%(n=20) had concurrent radiotherapy.

Demographic and clinical and histological characteristics of study population

The average age of participants was 48.86 years +/- 12.6, ranged from 18 to 81 years. Female gender predominated, accounting for 74% of cases, and 58% of patients were unemployed, as shown in Table I.

Table I: Demographic and clinical characteristics of study population. (N=100)

Variable	n	%
Gender		
Male	**26**	**26.0**
Female	**74**	**74.0**
Marital Status		
Married	**51**	**51.0**
Widow/Widower	**25**	**25.0**
Single	**22**	**22.0**
Divorced	**2**	**2.0**
Occupation		
Employed	**42**	**42.0**
Unemployed	**58**	**58.0**

Gynaecological cancers were the most common (47%) followed by digestive cancers 18% and 87% of patients were classified as regional (64%) or metastatic (23%) stage of disease. (See Table II)

Table II: Distribution of population according to clinical and histopathology characteristics (N=100)

Primary location	n	%
Gynaecological	47	47.0
Digestive	18	18.0
Head and neck	17	17.0
Breast	7	7.0
Others	11	11.0
Histology type		
Carcinoma	96	96.0
Sarcoma	2	2.0
Others	2	2.0
TNM Classification		
Localized	9	9.0
Regional	64	64.0
Distant spread	23	23.0

Therapeutic characteristics of study population

Sixty-four per cent of the study population received Highly Emetogenic platin based Chemotherapy (cisplatin) and and thirty-six per cent Moderately Emetogenic Chemotherapy (carboplatin and oxaliplatin). Antiemetic prophylaxis was given to every patient and 11% used oral care products before chemotherapy. The average number of cycles of chemotherapy received was 3.32 ±1.34. Table III presents the summary of therapeutics characteristics of the study population.

Table III: Distribution of population according to therapeutics characteristics (N=100)

	n	%
Chemotherapy Main Regimen		
Cisplatin	64	64.0
Carboplatin	25	25.0
Oxaliplatin	11	11.0
Premedication		
Antiemetics	100	100.0
Oral care products	11	11.0
Analgesics	3	3.0
Opioids	1	1.0
Antacids/anti-H_2	25	25.0
Cycle length		
weekly	24	24.0
2 weekly	3	3.0
3 weekly	73	73.0

Prevalence of gastrointestinal toxicity

Out of the 100 patients that participated in the study, 91% of patients had at least one GI-toxicity at a point in time before the next chemotherapy cycle and 9% of them had none. The individual prevalence of each clinical manifestations is shown in figure 1.

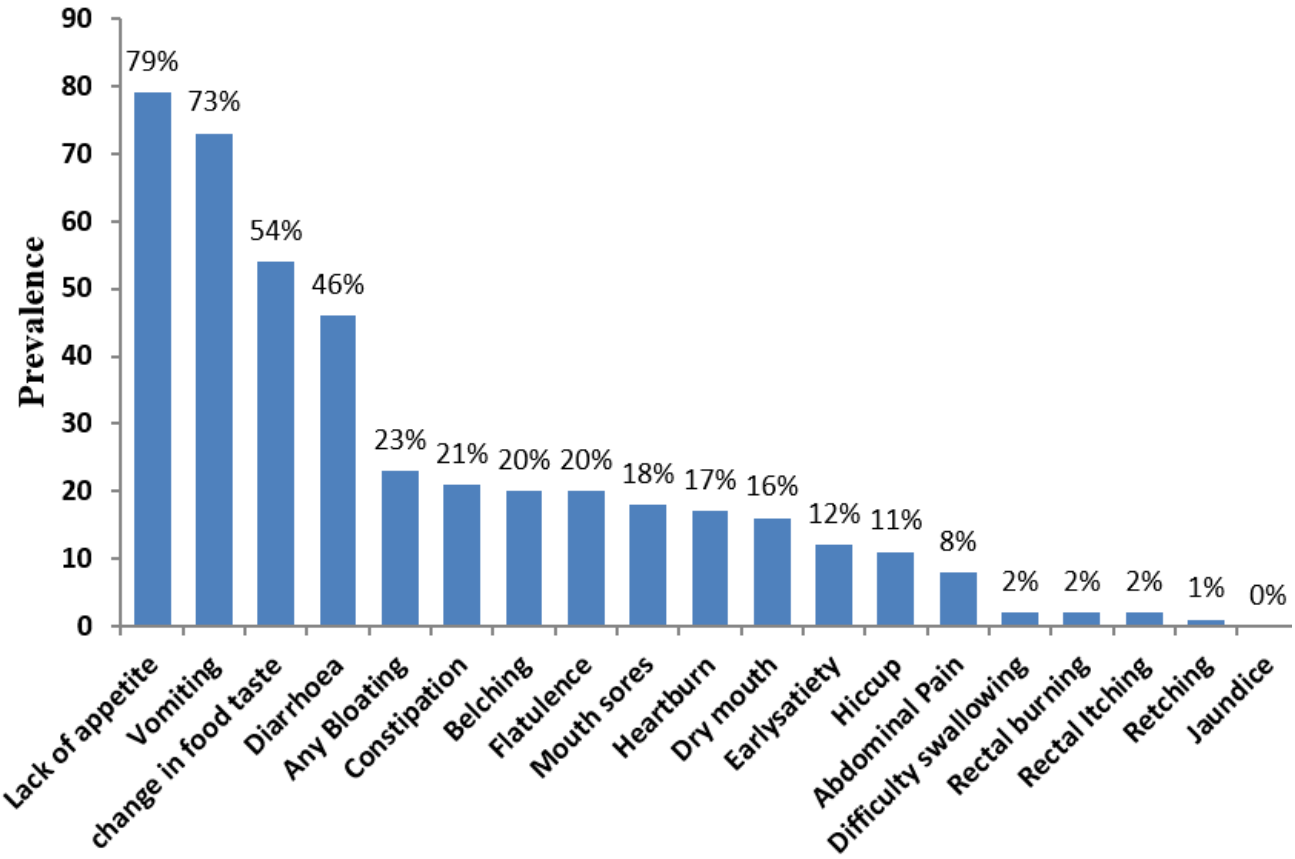

Figure 1: Prevalence of various GI clinical manifestations.

Types and grades of gastrointestinal toxicity

Most patients had grade I and II toxicity severity and only nausea/vomiting and diarrhoea had grade IV toxicity severity (see Table IV). Among grade I GI toxicities, the 5 most frequent were dysgeusia (28%), nausea and vomiting (25%), Bleching (20%), Anorexia (18%) and bloating (17%). Among grade II GI toxicities, the 5 most frequent were anorexia (61%), nausea and vomiting (32%), dysgeusia (26%), diarrhea (17%) and constipation (12%).

Table IV: Distribution of the study population according to toxicity types and their severities.

Clinical presentation	Grade 0 (%)	Grade I (%)	Grade II (%)	Grade III (%)	Grade IV (%)
Nausea and vomiting	**27.0**	**25.0**	**32.0**	**15.0**	**1.0**
Dry mouth	85.0	**11.0**	4.0		
Bloating	77.0	**17.0**	5.0	1.0	
Diarrhoea	54.0	14.0	17.0	11.0	4.0
Anorexia	21.0	**18.0**	**61.0**		
Dysphagia	98.0	2.0	0.0	0.0	0.0
Belching	80.0	**20.0**			
Retching	99.0	1.0			
Flatulence	80.0	**19.0**	1.0		
Heart burn	83.0	3.0	9.0	5.0	0.0
Abdominal pain	92.0	5.0	1.0	2.0	
Early satiety	88.0	7.0	1.0	4.0	
Rectal burning	98.0	2.0			
Rectal itching	98.0	2.0			
Hiccup	89.0	10.0	1.0		
Constipation	78.0	9.0	**12**.0	1.0	0.0
Mucositis	82.0	9.0	8.0	1.0	0.0
Dysgeusia	46.0	**28.0**	**26.0**	0.0	0.0
Jaundice	0.0	0.0	0.0	0.0	0.0

Clinical, epidemiological and therapeutic factors associated with GI toxicity

The frequency of occurrence of diarrhoea was significantly associated with age. It occurred in 63% of patients aged 40 years or over. All 19 clinical manifestations were more frequent in females than in males, however we found no significant association between gender and the occurrence of GI toxicities (see Table V). Concerning the association between treatment modality and the occurrence of GI toxicities, chemotherapy alone (58.3%) was significantly associated with the occurrence of an Early satiety with p-value of 0.045 (see Table VI). The prevalence of nausea/vomiting (p-value 0.024) and anorexia (p-value 0.001) were significantly higher with cisplatin while the prevalence of Rectal burning was significantly higher with carboplatin (p-value 0.047) as shown in table VII. We found significant associations between the number of cycles of chemotherapy and the occurrence of GI toxicity. In fact, bloating, belching, flatulence, early satiety and constipation were found to be more in patients who had more than 3 chemotherapy cycles (P-values at 0.005, 0.048, 0.048, 0.001and 0.023 respectively) as shown in Table VIII.

Table II: Association between age and toxicity.

Clinical presentation	Age < 40 years n (%)	Age ≥ 40 years n (%)	P-value
Nausea and vomiting	17 (23.3)	56 (76.7)	0.516*
Dry mouth	4 (25)	12 (75)	1.000[a]
Bloating	4 (17.4)	19 (82.6)	0.419[a]
Diarrhoea	17 (37)	29 (63)	0.011*
Anorexia	20 (25.3)	59(74.7)	0.887*
Dysphagia	0 (0.0)	2 (100)	1.000[a]
Belching	4 (20)	16 (80)	0.703[a]
Retching	1 (100)	0 (0.0)	0.250[a]
Flatulence	4 (20)	16 (80)	0.774[a]
Heart burn	6 (35.3)	11 (64.7)	0.282*
Abdominal pain	4 (50)	4 (50)	0.105[a]
Early satiety	4 (33.3)	8 (66.7)	0.488[a]
Rectal burning	0 (0.0)	2 (100)	1.000[a]
Rectal itching	0 (0.0)	2 (100)	1.000[a]
Hiccup	2 (18.2)	9 (81.8)	0.0726[a]
Constipation	3 (14.3)	18 (85.7)	0.264[a]
Mucositis	6 (33.3)	12 (66.7)	0.367*
Dysgeusia	15 (27.8)	39 (72.2)	0.487*
Jaundice			

***=P-value from X^2 test a=P-value from Fischer's exact test**

Table III: Association between treatment modality and toxicity

Clinical presentation	Chemotherapy alone n (%)	CCR n (%)	P-value
Nausea and vomiting	56 (76.7)	17 (23.3)	0.177*
Dry mouth	15 (93.8)	1 (6.4)	0.183[a]
Bloating	19 (82.6)	4 (17.4)	1.000[a]
Diarrhoea	37 (80.4)	9 (19.6)	0.920*
Anorexia	60 (75.9)	19 (24.1)	0.065[a]
Dysphagia	2 (100.0)	0 (0.0)	1.000[a]
Belching	16 (80.0)	4 (20.0)	0.881[a]
Retching	1 (100.0)	0 (0.0)	1.000[a]
Flatulence	18 (90)	2 (10)	0.348[a]
Heart burn	16 (94.1)	1 (5.9)	0.182[a]
Abdominal pain	7 (87.5)	1 (12.5)	1.000[a]
Early satiety	7 (58.3)	5 (41.7)	0.045*
Rectal burning	2 (100.0)	0 (0.0)	1.000[a]
Rectal itching	1 (50.0)	1 (50.0)	0.362[a]
Hiccup	10 (90.9)	1 (9.1)	0.456[a]
Constipation	17 (81.0)	4 (19.0)	1.000[a]
Mucositis	15 (83.3)	3 (16.7)	1.000[a]
Dysgeusia	42 (77.8)	12 (22.2)	0.547*
Jaundice	0 (0.0)	0 (0.0)	

*=P-value from X^2 test a=P-value from Fischer's exact test CCR= concurrent chemoradiotherapy

Table IV: Association between specific platin drug used and toxicity

Clinical presentation	Cisplatin n(%)	Carboplatin n(%)	Oxaliplatin n(%)	P-value
Nausea and vomiting	52 (71.2)	16 (21.9)	5 (6.8)	0.024
Dry mouth	10 (62.5)	6 (37.5)	0 (0.0)	0.193
Bloating	15 (65.2)	6 (26.1)	2 (8.7)	0.921
Diarrhoea	31 (67.4)	12 (26.1)	3 (6.5)	0.418
Anorexia	54 (68.4)	21 (26.6)	4 (5.0)	0.001
Dysphagia	2 (1.00)	0 (0.0)	0 (0.0)	0.563
Belching	13 (65.0)	6 (30.0)	1 (5.0)	0.378
Retching	1 (100.0)	0 (0.0)	0 (0.0)	0.753
Flatulence	14 (70.0)	4 (20.0)	2 (10.0)	0.813
Heart burn	11 (64.7)	5 (29.4)	1 (5.9)	0.723
Abdominal pain	7 (87.5)	1 (12.5)	0 (0.0)	0.325
Early satiety	9 (75.0)	2 (16.7)	1 (8.3)	0.696
Rectal burning	0 (0.0)	2 (100.0)	0 (0.0)	0.047
Rectal itching	2 (100.0)	0 (0.0)	0 (0.0)	0.563
Hiccup	7 (63.6)	4 (36.4)	0 (0.0)	0.368
Constipation	12 (57.1)	6 (28.6)	3 (14.3)	0.744
Mucositis	12 (66.7)	5 (27.8)	1 (5.6)	0.710
Dysgeusia	37 (68.5)	14 (25.9)	3 (5.6)	0.167
Jaundice	0 (0.0)	0 (0.0)	0 (0.0)	

Table V association between cycle number and toxicity

Clinical presentation	3 or less n (%)	More than 3 n (%)	P-value
Nausea and vomiting	44 (60.3)	29 (39.7)	0.202
Dry mouth	7 (43.8)	9(56.2)	0.066
Bloating	9 (39.1)	14 (60.9)	0.005
Diarrhoea	29 (63.0)	17 (37.0)	0.854
Anorexia	47 (59.5)	32 (40.5)	0.069
Dysphagia	1 (50.0)	1 (50.0)	0.677
Belching	9 (45.0)	11 (55.0)	0.048
Retching	1(100)	0 (0.0)	0.451
Flatulence	9 (45.0)	11 (55.0)	0.048
Heart burn	9 (52.9)	8 (47.1)	0.297
Abdominal pain	5 (62.5)	3 (37.5)	0.927
Early satiety	2 (16.7)	10 (83.3)	0.001
Rectal burning	1 (50.0)	1 (50.0)	0.677
Rectal itching	1 (50.0)	1 (50.0)	0.677
Hiccup	6(54.5)	5 (45.5)	0.489
Constipation	9 (42.9)	12 (57.1)	0.023
Mucositis	9 (50.0)	9 (50.0)	0.172
Dysgeusia	36 (66.7)	18 (33.3)	0.547
Jaundice	0 (0.0)	0 (0.0)	

DISCUSSION

Prevalence of GI-toxicity

The results of this study shows that the general prevalence of gastrointestinal toxicity is 91% meaning that 91% of patients had at least one gastrointestinal clinical manifestation post chemotherapy. This high prevalence is in accordance with previous studies which concluded that GI toxicity is one of the most common side effects of chemotherapy if not the first [2,3, 9].

The participants had a variety of clinical manifestations, a total of 18 that were present at least once with their individual prevalence as follows; anorexia (79%), nausea & vomiting (73%), dysgeusia (54%), diarrhoea (46%), bloating (23%), constipation (21%), belching (20%), flatulence (20%), Mucositis (18%), heart burn (17%), xerostomia (16%), early satiety (12%), hiccup (11%), abdominal pain (8%), dysphagia (2%), rectal burning (2%), rectal itching (2%), and retching (1%). This result is similar to a study done by Cherwin et al in USA which showed that chemotherapy causes many GI side effects and Boussios et al in Greece who reported most of the above clinical presentations [2,4,5] but contrary to Cazin JL et al in France who reported only 3 of those (nausea/vomiting, diarrhoea and mucositis) [10].

The prevalence of Anorexia, which was the most frequent clinical manifestation (79%) was found to be higher than the one reported by Boussios et al (29%) [2]. It was also reported as being one of the most common in advanced cancer by Davis et al [11]. Could this difference be explained by the presence of other factors that are often not taken into account in low-income countries, such as the psychological distress associated with cancer, which is often a source of anorexia?

Nausea/vomiting were second most common with an overall prevalence of 73%, despite the use of preventive measures. a similar conclusion has been made by Pirri et al in their study in Australia where they found that 62% of patients receiving HEC and MEC had nausea and vomiting [12]. Platinum salts are known to be emetogenic, and cisplatin, which is the most emetogenic, was the most commonly used drug in our study (81.2%). In addition, the recommended combinations of antiemetics (setrons, aprepitant, corticoids) in the premedication of platinum-based chemotherapy were not always available in our socio-economic context.

The frequency of dysgeusia, was 54%, and found to be lower than the 75% of taste and smell changes reported by Bernhardson et al. In the other hand, he also found it to be independent from chemotherapy regimen used [13]. Ijpma et al in Netherland reported that only 15% of participants in their study who received platin based regiments reported a metallic taste [14]. Zabernigg et al also reported taste change to be high in chemotherapy (69.9%) but very low in platin based regiments[15]. The onset of dysgeusia is generally linked to damage to the taste buds by cytotoxic drugs. However, good supportive care through nutritional advice and tips can help patients cope.

Toxicity severity

Severity of GI toxicity was found to vary from grade 0 (absent) to grade 4 (life threatening). Majority of patients (97.4%) had less than grade 3 toxicity severity for all clinical manifestations and only nausea/vomiting (1%) and diarrhoea (4%) were life threatening (grade 4 severity). The majority of these grade 3 and 4 toxicities occurred in patients receiving Cisplatin; Devisetty et al in their series report results similar to ours [16]. This highlights the importance of premedication taking into account the emetogenic potential of anticancer drugs, and also the need to anticipate the occurrence of these toxicities in order to prevent life threatening complications [17,18]. In Douala General Hospital, patients were given a list of medications to take in case of any side effect. This could explain why most had less than grade 3 severities.

Associated factors to toxicity

With regards to age as an associated factor for GI toxicity, older age (> 40 years) was identified as a significant risk for the development of chemotherapy-induced diarrhoea (CID) (p-value <0.011). With regards to gender as associated factor for GI toxicity, all clinical manifestations were higher in females but there was no statistical significance for these differences. This is similar to results of Eskinder Ayalew Sisay in Ethiopia which also found no association between gender and the occurrence of chemotherapy-induced toxicities [19].

With regards to therapeutic factors associated to GI toxicities, treatment modality was significantly associated with early satiety (p-value <0.045); Cisplatin was found to be more emetogenic than carboplatin and oxaliplatin (P<0.024) as described in literature [20,21]. Anorexia was also more frequent with cisplatin than the others (P= 0.001). According to Bouganim and al in Ottawa, nausea and vomiting were found to occur more in patients who had experienced chemotherapy before [20,21,22,] but it was not the case in this study. We found an association between the occurrence of GI toxicities and the number of cycles of chemotherapy (flatulence, bloating, belching, early satiety and constipation were significantly found to be more in patients who had more than 3 chemotherapy cycles).

Cancer stage was also evaluated for association to GI toxicity but was not found to be associated to any toxicity.

CONCLUSION

The prevalence of gastrointestinal toxicity with platinum-based treatment regimens at the oncology unit of Douala General Hospital was found to be high. Anorexia, nausea and vomiting and dysgeusia were found to be the 3 most frequent GI toxicities. The grade I and II GI toxicities were the most common. There was an association between the age, the treatment modality, the type of platinum salts used, the number of cycle of chemotherapy received and the occurrence of GI toxicities.

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Conflicts of interest

The authors declared no conflict of interest at the time the study was carried out.

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