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Gastric cancer treatment and its association with nephrotoxicity

A terapêutica do câncer gástrico e sua associação com a nefrotoxicidade

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ABSTRACT: Gastric cancer has been affecting Brazilians, especially men and the population over the age of 55 years thus being a relevant thematic in the scope of health promotion. This neoplasm can exhibit comorbidities resulting from tumors or therapeutics, generating obstacles for the prognostic of patients, such as nephrotoxicity. Thus, the analysis between the variations in the levels of creatinine and urea versus the presence of oncological treatment, tumor histology, sex, ethnicity and age of patients with gastric cancer treated at the Hospital Regional do Câncer in Passos between January 2012 and December 2015 was proposed. The present study is a cross-sectional observational study with data obtained from a documentary source. Considering creatinine, among patients undergoing some type of treatment, 95.3% presented variation in creatinine levels and this difference was significant from the statistic point of view (p = 0.042). Regarding urea levels 93.7% of patients showed variations, although without significant difference (p=0.147). The conclusion was that the presence of any treatment in patients with gastric cancer can alter serum creatinine levels, evidencing the importance of its monitoring for the promotion of comprehensive patient care.

Keywords: Creatinine; Stomach neoplasms; Urea; Combined modality therapy; Kidney.

RESUMO: O câncer gástrico vem acometendo os brasileiros, sobretudo os homens e a população com idade superior a 55 anos, sendo, portanto, temática relevante na promoção do cuidado. Essa neoplasia pode apresentar comorbidades decorrentes do tumor ou terapêutica, gerando entraves no prognóstico do paciente, como a nefrotoxicidade. Assim, propõe-se analisar associações entre a variação dos níveis de creatinina e ureia versus a presença de tratamento oncológico, histologia do tumor, sexo, etnia e idade dos pacientes com câncer gástrico atendidos no Hospital Regional do Câncer de Passos, no período de janeiro de 2012 a dezembro de 2015. Trata-se de um estudo observacional transversal com dados obtidos em fonte documental. Considerando a creatinina, notou-se que dentre os pacientes que realizaram algum tipo de tratamento, 95,3% apresentaram variações dos níveis de creatinina e esta diferença foi significativa do ponto de vista estatístico (p=0,042). De acordo com os níveis de ureia, 93,7% dos pacientes apresentaram variações, entretanto sem diferença significativa (p=0,147). Conclui-se que a presença de qualquer tratamento nos pacientes com câncer gástrico pode alterar os níveis séricos de creatinina, evidenciando assim a importância do monitoramento destes para promover o cuidado integral do paciente.

Palavras-chave: Creatinina; Câncer gástrico; Ureia; Terapia combinada; Rim.

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INTRODUCTION

The National Cancer Institute[1] estimates 21,230 new cases of gastric cancer for the year 2020, being 13,360 in men and 7,870 in women, and making it the third most frequent type of cancer among men and the fifth among women. Furthermore, statistics point to a higher incidence among those over 50 years of age. According to data from the Ministry of Health[2], the predominant histological types are: adenocarcinoma, lymphoma and leiomyosarcoma. The most prevalent adenocarcinoma has a multifactorial cause, including both environmental and genetic aspects.

Gastric cancer has its prognosis and treatment guided by the location and staging of the tumor, the number of resected and affected lymph nodes and the presence of metastases. It may appear diffusely in the organ, be located in the proximal portion of the stomach, involving or not the gastroesophageal junction, or in the most distal portion, close to the pylorus[2]. The current knowledge acquired about the pathophysiology of gastric cancer can provide support for the proper treatment, management, prevention and early diagnosis.

Treatment depends on the patient's condition, early discovery of the condition, age, general health and individual circumstances. The available options include surgeries, chemotherapy regimen, target therapy and radiotherapy, as well as a combination of therapies[3].

Chemotherapy and radiotherapy stand out among the treatment modalities for this neoplasm. Chemotherapy is the most used method and consists of a set of chemotherapy aimed at targeting abnormal cells. Unfortunately, these chemotherapeutics can affect cells with normal functioning, generating harmful effects to the body, called toxic effects of chemotherapeutics, found mainly in methotrexate, cisplatin and ifosfamine[4,5]. Cisplatin is a chemotherapeutic often used to treat stomach cancer, although it can result in oxidative stress, which plays a key role in kidney damage[6,7]. Toxicity depends on the time of exposure to the drug and its concentration. The main toxic effects observed in cancer patients undergoing chemotherapy are: anemia, gastrointestinal diseases, alopecia and nephrotoxicity. As for this last effect, it is known that chemotherapy can lead to renal damage mainly due to acute tubular necrosis and thrombotic microangiopathy, among other manifestations[8].

Radiotherapy is a method that can destroy tumor cells using a beam of ionizing radiation. A pre-calculated dose of radiation is applied at a given time to a volume of tissue encompassing the tumor in order to destroy all tumor cells with as little damage as possible to normal cells. Unfortunately, this therapeutic modality has side effects classified as late and immediate. Immediate effects are observed in tissues with greater proliferative capacity, such as the gonads, epidermis, mucous membranes of the digestive, urinary and genital tracts, and bone marrow[9,10].

Chen et al.[11] demonstrated that during radiotherapy in older adults, the irradiating area of treatment in patients already treated or undergoing treatment with nephrotoxic drugs deserves attention, as the simultaneous or sequential irradiation of one or both kidneys, even if inadvertently, may cause additional irreparable kidney damage.

As a result of nephrotoxicity, renal involvement can be caused either by the therapy or as a result of cancer itself. The pathophysiology of this nephrotoxicity varies widely and can manifest as chronic kidney disease or acute kidney injury. The latter can come from infections, hypovolemia (caused by vomiting or diarrhea in cancer treatment settings), hypercalcemia (seen in 30% of cancer patients), hepatorenal syndrome (infiltration of tumor cells in the liver), accumulation of chemotherapy drugs such as cisplatin, anemia secondary to cancer and its treatment, tumor infiltration in the kidneys and other causes. Acute kidney injury can progress to chronic kidney disease, as it usually occurs in non-cancerous patients[12].

By means of a simple and quick analysis of some laboratory tests such as urea and serum creatinine, it is possible to assess the renal activity, aiming at the diagnosis and early treatment of renal damage[10,13].

The focus given to the incidence of changes in creatinine and urea levels in patients with gastric cancer is justified by data in the literature[14,15,16], which show that patients with neoplastic diseases, including gastric cancer, present variations in such parameters due to therapy and/or neoplasia, suggesting nephrotoxicity. As treatment interruption in cases of acute kidney injury is the main approach, this possible side effect limits cancer treatment and interferes with the patient's prognosis and quality of life. In addition, the gastric tumor itself can lead to renal damage, whether due to paraneoplastic renal manifestation, need for nephrectomy and/or urinary tract obstruction[17]. Thus, the aim was to analyze the possible associations between the occurrence of variation in serum levels of creatinine and urea versus the presence of cancer treatment, histological type of tumor, gender, ethnicity and age of patients with gastric cancer treated at the *Hospital Regional do Câncer* located in the city of Passos, state of Minas Gerais (MG) between January 2012 to December 2015.

MATERIAL E METHODS

An observational cross-sectional study conducted from March 2018 to January 2020. Data from all patients with gastric cancer treated at the *Hospital Regional do Câncer i*n Passos-MG between January 2012 and December 2015 were evaluated. The period was chosen based on a pilot study that addressed the number of cases of gastric cancer at the *Hospital Regional do Câncer* in Passos-MG and the histological types in the period from January 2012 to December of 2015[18]. This study was approved by the Research Ethics Committee under protocol number

3.333.161. Information regarding the variables of creatinine and urea, therapeutic modality (surgical treatment, chemotherapy, radiotherapy and combinations between these modalities), histological type, gender, ethnicity and age were obtained from the medical records and the Registry and Internal Statistics System of the *Hospital Regional do Câncer*.

Two isolated measures of urea and creatinine were evaluated; one at the time of diagnosis and the other at the end of the patient's follow-up treatment. For statistical analysis, the variation in urea and creatinine values was categorized considering the cutoff point of 50% variation. Patients who had a variation less than 50% were allocated to one group and patients who had a variation greater than or equal to 50% were included in another group. For statistical analysis, the SPSS 19.0 software was used. To assess the homogeneity of the sample, the Levene's test was used. For statistical comparison between two groups, the Student's t test was used when variables were quantitative and homogeneously distributed, and the chi-square test for qualitative variables. In all statistical analysis, a significance level of 5% was adopted, that is, results that presented p-value less than 5% ($P < 0.05$) were considered statistically significant.

RESULTS

The medical records of 101 patients with gastric cancer were analyzed. Among the 101 patients, 73.3% (74) were male and 26.7% (27) were female. It was observed that 83.8% (62) of men affected by gastric cancer had variations greater than or equal to 50% in creatinine levels and 95.9% (71) in urea levels. Likewise, 85.2% (23) of women with gastric cancer showed variation in creatinine levels and 96.3% (26) in urea levels (p=0.864; p=0.936 respectively).

The average age was 64 years old, minimum of 31 and maximum of 86 years. The study showed that patients with variation in creatinine had a mean age of 65.18 years (SD: ±13.581) and among patients with variation in urea, the mean age was 64.7 years (SD: ±13.140). For patients who did not show a change in creatinine, the mean age was 61.5 years (p=0.308) and for those who did not show a change in urea it was 62 years (p=0.690).

Among the patients analyzed, 55% were white people, of which 83.6% had variation in creatinine and 98.2% had variation in urea.

As for the black population, 6% of patients, 100% showed variation in creatinine and 66.7% in urea. The yellow race represented 3% of patients and in 100% of them, there was variation in creatinine and urea. Among mixed race patients, 36% of patients, 80.6% had a variation in creatinine and 97.2% had a variation in urea. No statistical significance was found for the analysis of creatinine variation (p=0.565), although we found significant differences when the variation in urea was evaluated according to ethnicity (p=0.002).

The most prevalent histological type in this study was adenocarcinoma, found in 66.3% (67) of patients. Among patients affected by adenocarcinoma, 82.1% (55) had variation in creatinine levels and 97% (65) in urea levels, with no statistical differences observed (p=0.424; p=0.480 respectively).

Regarding treatment, patients were categorized into two groups; in the first group, any type of treatment was considered, and in the second group, patients who did not undergo treatment for gastric cancer were included. The analysis showed significant differences for the variation in creatinine (Table 1). As for creatinine and urea values, 95.3% of patients who underwent some type of treatment had variation in creatinine levels (p=0.042) and 93.7% had variation in urea (p=0.147).

However, when statistical analysis was performed for each type of treatment in isolation, we did not find statistically significant differences. Among patients analyzed, there was a variation in creatinine levels in 56.5% (48) of patients who underwent surgical treatment (p=0.65), 22.4% (19) of those who underwent radiotherapy (p=0.443) and 68.2% (58) of those who underwent chemotherapy (p=0.352). According to urea levels, we also did not find significant differences when we subdivided patients according to type of treatment. We found variation in urea levels in 57.7% (56) of patients who underwent surgical treatment (p=0.759), 22.7% (24) of those who underwent radiotherapy (p=0.255) and 67% (65) who underwent chemotherapy (p=0.480).

Table 1. Variation of creatinine values in relation to the presence or absence of treatment.

Creatinine variation	Did you undergo treatment?		P value
	Yes	No	
No	81.2% (13)	18.8% (3)	**0.042***
Yes	**95.3% (81)**	4.7% (4)	

* Chi-square test

DISCUSSION

The treatment of gastric cancer and the presence of changes in renal activity may have a significant relationship, considering the nephrotoxicity associated with the therapy and the patient's clinical condition. In this study, it was evident that 95.3% of patients with gastric cancer who underwent any treatment had variation in creatinine levels and 93.7% had variation in urea levels. This variation was also observed in the study by Visacri[19], who noted that 89.83% of cancer patients undergoing chemotherapy and radiotherapy treated at the *Hospital das Clínicas* of the *Universidade Estadual de Campinas* had higher serum creatinine levels after the first chemotherapy cycle. Brito et

al.[16] showed that 29.6% of cancer patients, including gastric cancer, undergoing chemotherapy and/or radiotherapy had high serum creatinine, accounting for 31.6% of men and 25% of women.

In addition, our findings demonstrate that more than 65% of patients undergoing chemotherapy showed changes in the biochemical parameters analyzed, corroborating the study by Peixoto[4], in which 82.35% of cancer patients undergoing chemotherapy showed variation in creatinine levels after chemotherapy. Similarly, Mattiello et al.[20] demonstrated that cisplatin and methotrexate, drugs routinely used in chemotherapy, are frequently associated with kidney damage, which can lead to acute kidney injury that is initially indicated by an isolated increase in serum creatinine. These data are corroborated in a literary review by Peres et al. [21], which demonstrated that 25 to 35% of cancer patients treated with a simple dose of cisplatin had worsening of renal function associated with higher creatinine levels.

Cancer treatment can change the renal function of patients either by direct kidney injury due to nephrotoxicity or by irradiation during radiotherapy[22]. In addition, previous kidney diseases and the use of non-chemotherapeutic nephrotoxic drugs also corroborate this change. In this sense, the monitoring of renal activity from substances such as urea and serum creatinine is important in cancer patients for the safe handling of therapeutic agents in order to expand the care provided to them[14].

Our findings also revealed that most patients evaluated in the study were male (73.3%), corroborating the study by Arregui et al.[23]. The mean age of patients analyzed was 64 years, similar to estimates by the National Cancer Institute, thus, we emphasize the need for monitoring plasma urea and creatinine in this population, since the estimated glomerular filtration rate declines in parallel with age[19,24].

Among the ethnic groups observed, the white population was the most affected (55%), corroborating data observed by Ramos[25], who showed a twice as high frequency of the tumor in question in the white population.

As for characteristics of the tumor, there was a prevalence of adenocarcinoma (66.3%). According to the National Cancer Institute, the histological type adenocarcinoma is responsible for about 95% of cases of stomach tumors[9].

In this sense, the narrowing of the base of the population's age distribution pyramid, which shows the aging of the Brazilian and world population, highlights the importance of expanding the care offered to this group. Furthermore, nephrologists, oncologists and the entire multidisciplinary team assisting patients with gastric cancer should be aware of the nephrotoxicity of cancer treatment, not only to prevent and treat long-term kidney damage, but also for epidemiological, pharmacological and therapeutic reasons. A rigorous monitoring of plasma urea and creatinine values is suggested for better management, prevention and comprehensive cancer patient care.

CONCLUSIONS

In the study, most patients with gastric cancer were men around 64 years of age and adenocarcinoma was the most prevalent type of tumor. Furthermore, the presence of treatment for these patients, regardless of the modality adopted, was associated with changes in serum creatinine levels. Further studies are needed to better understand this finding.

Collaborations: Nathália Pereira Alves, Yara Paschoal de Souza, Sabrina Thalita dos Reis Faria and Natael Ribeiro Malta Neto participated in the collection, analysis and interpretation of data. Nathália Pereira Alves and Camila Belfort Piantino wrote the first version of the manuscript. All authors approved the final version.

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