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RETROSPECTIVE ANALYSIS OF NEPHROTOXICITY BY CISPLATIN IN PATIENTS WITH CANCER OF CERVIX DURING THE TREATMENT OF CISPLATIN AND CONCURRENT RADIOTHERAPY

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ABSTRACT

PURPOSE: To evaluate acute renal toxicity during the simultaneous administration of cisplatin-radiotherapy as treatment in cervical cancer in women under and over 50 years.

METHODS: Women with a diagnosis of cervical cancer with clinical stage IB1 to IVA, and even patient with clinical stage IVB who after systemic treatment had persistent disease locally, treated with Radiotherapy and weekly cisplatin. It was grouped into adults over and under 50 years old to evaluate the incidence of renal failure according to the age of decrease in physiological glomerular filtration rate. In whom a retrospective - descriptive statistical analysis was performed with the program SPSS V.21, EXCEL 2010 and "R" program, to compare the stages of weekly AKIN globally regardless of age and dividing into women under and over 50 years old. The ANOVA test was applied to compare the weekly creatinine levels globally in the entire study group and separate them into groups of people under and over 50 years old. The Friedman test and the Kruskal Wallis test were applied with an alpha of 0.05 in order to compare the weekly AKIN stages globally regardless of the ages as well as lost patients under the SPSS program.

RESULTS: Using the Friedman test (alpha = 0.05 and a confidence interval of 95%) according to the AKIN scale, a non-significant value ($p = 0.477$) was obtained, so there is no increase in the incidence of acute renal failure in the studied population. With the Kruskal Wallis test, measuring the difference of acute renal failure and taking the population as a whole, a value of ($p = 0.599$) was obtained. When comparing women under and over 50 years old in regard to the incidence of acute renal failure, taking into account the aging process in renal physiology, a value of ($p = 0.118$) was obtained for the group under 50 years old and a value of ($p = 0.6014$) for the group over 50 years old.

CONCLUSION: Age greater than 50 years, although it seems to have a greater tendency to present renal involvement during treatment, at the moment at standard doses of treatment, does not present a major effect, however, renal function must be constantly monitored and looked after.

KEYWORDS : Cisplatin, radiotherapy, cancer, cervix, nephrotoxicity, age

INTRODUCTION.

Since its discovery, cisplatin has become the cornerstone of chemotherapeutic treatment in solid tumors, despite its adverse effects described as nephrotoxicity and ototoxicity which limit its use or make it necessary to adjust the dose. (2-9) Concurrent chemo radiotherapy is considered the standard treatment for cervical cancer patient Ib2 to IVA clinical stage, the base of this chemotherapy treatment is Cisplatin that acts as a radio-sensitizer to the treatment of external beam radiotherapy.

At the renal level, cisplatin is secreted and concentrated by the membrane transporters, the high affinity copper transporter 1 (CTR1) and the organic cation transporter (OCT2) located in the basement membrane of the proximal tubule cells. Several molecular mechanisms of cisplatin nephrotoxicity have been described, such as the role of microRNAs that interact with the representative members of a wide range of regulatory pathways of proliferation, inflammation, and fibrosis. Induces the production and release of oxygen free radicals (ROS) and inhibits antioxidant enzymes causing injury by oxidative stress. It increases the expression of tumor necrosis factor alpha and the expression of inducible proteins of nitric oxide synthase (iNOS) causing apoptosis of tubular cells. These mechanisms produce a mitochondrial dysfunction, decrease in ATPase activity, alter the transport of solutes together with the balance of cations, clinically expressing as polyuria with an increase in the excretion of salt and magnesium, developing a self-limited salt-losing nephropathy at 2- 4 months of the initial dose of cisplatin (6,8,10,11)

The prevention of cisplatin-induced nephrotoxicity is aimed at reducing the concentration of the drug in the blood, limiting the time of exposure to the renal tubules, for which high-volume hydration, forced diuresis and magnesium supplementation are recommended (8)

Taking into account the decrease in glomerular filtration rate by age,

with tubulointertial fibrosis seen in renal microvascular disease, measuring fractional excretion of magnesium as a sensitive biomarker that reflects an early stage of renal fibrosis (9) showing that from 45 to 50 years, the glomerular filtration rate is lost between 1 and 1.5 ml / min. At the moment there are no studies that describe the relationship of the physiological decrease in the glomerular filtration rate with the incidence of acute renal failure secondary to the administration of cisplatin (10)

The main objective of this study is to determine the incidence of acute renal failure in patients who have received cisplatin-based chemotherapy and concomitant radiotherapy, and as a secondary objective to determine the relationship between age and acute renal failure secondary to the use of cisplatin.

METHODS

Data from electronic medical records were collected from 2014 - 2015 of women over 18 years of age who received concurrent Radiotherapy-Cisplatin treatment at the Solón Espinosa Ayala Oncology Hospital (SOLCA), Quito core, with diagnosis of cervical cancer, clinical stage IB2 to IVA, and those women with clinical stage IVB who, after receiving systemic chemotherapy, had persistence of local disease in whom treatment with concurrent cisplatin-radiotherapy was completed.

TYPE OF STUDY

A historical cohort of women over 18 years of age with a diagnosis of cervical cancer IB2 to IVA-IVB clinical stage who were receiving chemotherapy treatment with weekly Cisplatin in concomitance with external beam radiotherapy with baseline serum creatinine measurement was performed and weekly measurements until treatment is complete. It was grouped into adults and children under 50 years of age to evaluate the incidence of renal failure according to the age of decrease in physiological glomerular filtration rate.

POPULATION

Patients women over 18 years of age hospitalized at the Solón Espinosa Ayala Oncology Hospital Quito from 2014 to 2015 with a diagnosis of cervical cancer Ib1 clinical stage to IVA and even IVB after systemic treatment with persistence of local disease, patients had to have before of receiving treatment a platelet count greater than 100,000 U / l, Hemoglobin greater than 10 G / dl and neutrophil count greater than 1500 mm3, serum creatinine value the day before or the same day to the administration of weekly cisplatin, to dose of 40 mg / m2 on days 1, 8, 15, 22 and 29, while possible, its administration 2 hours prior to concomitant external beam radiotherapy at a dose of 50.4 Gys; The institutional nephroprotection protocol includes administration of high intravenous volumes of 0.9% sodium chloride prior to the administration of chemotherapy plus 10 mg of intravenous furosemide after the administration of Cisplatin.

Were excluded women with a history of renal failure under treatment, women with a glomerular filtration rate of less than 40ml / min or bilateral grade 4 hydronephrosis confirmed by imaging.

Acute renal failure was determined according to the AKIN scale based on the kinetics of serum creatinine levels, categorizing them into three phases. AKIN 1 defined by an increase in serum creatinine of ≥0.3mg / dl or 1.5 times its baseline value, AKIN 2 corresponds to the increase in serum creatinine value in 2N in relation to its baseline creatinine value and AKIN 3 corresponds to the increase in serum creatinine value in 3N in relation to its baseline creatinine value. (11,12)

STATISTIC ANALYSIS

A descriptive analysis was made with the variables collected and a statistical analysis with the SPSS program version 21 and EXCEL 2010 to compare the weekly AKIN stages in a global form regardless of the ages and dividing into over and under 50 years. The ANOVA test was applied to compare the weekly creatinine levels of a global form in the entire study group and separate them into groups of people under and over 50 years old. The Friedman test and the Kruskal Wallis test were applied with an alpha of 0.05 to compare the weekly AKIN stages in a global form regardless of the ages, patients lost under the SPSS program, divided into under and over 50 years.

RESULTS

We retrospectively analyzed a total of 160 individuals with confirmed diagnosis of cervical cancer IB1 clinical stage to VAT, as well as those patients with clinical stage IVB who after receiving systemic treatment (Paclitaxel-Carboplatin), remained with local persistence of disease and took concurrent local treatment with cisplatin-radiotherapy. Of the total of patients, 82 patients corresponded to an age younger than 50 years and 78 patients to an age older than 50 years. The frequency of distribution of renal failure assessed by AKIN by clinical stage as well as by age are summarized in Table 1.

Table 1. Descriptive analysis of women who received concurrent cisplatin-radiotherapy.

VARIABLE			N	%	p
AGE	<50 años		82	51,2	
	>50 años		78	48,8	
			160	100	
CLINICAL STAY	EC IB1		2	1,3	
	EC 1B2		2	1,3	
	EC IIA		5	3,1	
	EC IIB		51	31,9	
	EC IIIA		10	6,3	
	EC IIIB		71	44,4	
	EC IVA		2	1,3	
	EC IVB		14	8,8	
	EC X		3	1,9	
	TOTAL		160	100	
AKIN WEEK 1	< 50 YEARS	NORMAL	78	96,3	0,041
		AKIN 1	2	2,5	
		AKIN 2	1	1,2	
		AKIN 3	0	0	
			81		
			LOST 83		
	50 YEARS	NORMAL	66	85,7	
		AKIN 1	10	13	
		AKIN 2	0	0	
		AKIN 3	1	1,3	
			LOST 78		
AKIN WEEK 2	< 50 YEARS	NORMAL	75	97,4	0,11
		AKIN 1	1	1,3	
		AKIN 2	1	1,3	
		AKIN 3	0	0	
			77		
			LOST 4		
	50 YEARS	NORMAL	59	84,3	
		AKIN 1	10	14,3	
		AKIN 2	1	1,4	
		AKIN 3	0	0	
			70		
			LOST 8		
AKIN WEEK 3	< 50 YEARS	NORMAL	50	96,2	0,8
		AKIN 1	1	1,9	
		AKIN 2	1	1,9	
		AKIN 3	0	0	
			52		
			LOST 20		
	50 YEARS	NORMAL	47	94	
		AKIN 1	2	4	
		AKIN 2	1	2	
		AKIN 3	0	0	
			50		
			LOST 28		

AKIN WEEK 4	LESS THAN 50 YEARS	NORMAL AKIN 1 AKIN 2 AKIN 3	39 4 0 1	88,6 9,1 0 2,3	0,25
			44 LOST 38		
	ABOVE THAN 50 YEARS	NORMAL AKIN 1 AKIN 2 AKIN 3	35 1 0 3	89,7 2,6 0 7,7	
			38 LOST 40		
AKIN WEEK 5	LESS THAN 50 YEARS	NORMAL AKIN 1 AKIN 2 AKIN 3	31 0 0 0	100	0,26
			31 LOST 50		
	ABOVE THAN 50 YEARS	NORMAL AKIN 1 AKIN 2 AKIN 3	29 2 1 1	89,7 6,1 3 3	
			33 LOST 45		

It is important to note that 44.4% of the patients during this period of time were diagnosed in clinical stage IIIB, followed by the clinical stage IIB. It is interesting to observe how 8.8% of the women in clinical stage IVB with persistence of disease who received systemic chemotherapy could be taken to concomitant treatment.

In the same way, a graphical analysis of dispersion of serum creatinine values per weeks represented in Figure 1 was carried out, It is striking that most patients do not have a significant movement of serum creatinine values, however at week 3, two important creatinine elevations can be seen with serum creatinine values of up to 5 mg / dL.

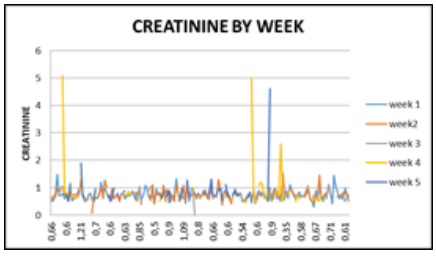

Figure 1. Serum creatinine distribution per week

This analysis of point distribution was completed by assessing acute renal failure per week in relation to clinical stage, it is important to note that this kidney damage is seen immediately during the first 2 weeks, with stages IIB and IIIB representing the higher degree of damage, the first week is excluded since in theory they had good renal function, and those patients who presented acute kidney disease were due to an obstructive renal process that was immediately evident.

Kidney disease in stages IIB and IIIB may have to be associated with hydronephrosis as an adjuvant trigger, these data are represented in Figure 2.

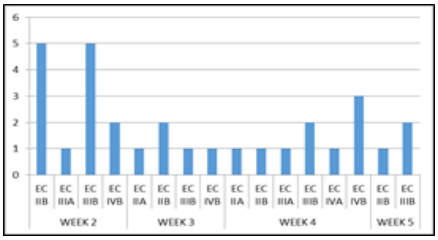

Figure 2: Distribution of renal insufficiency per week according to the clinical stage

While AKIN 1 renal failure occurs more frequently in the first weeks, these are more affected at weeks 3 and onwards, AKIN 2 and AKIN 3 are presented more frequently in these weeks, as shown in Figure 3.

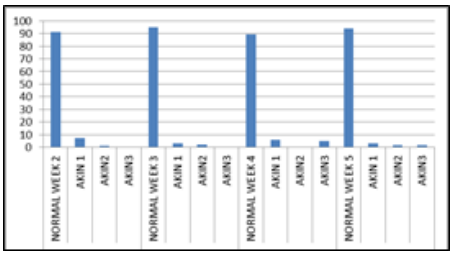

Figure 3. Distribution of renal failure by weeks

At week 2 of treatment, which is the week in which if we can assess a renal failure, we can see that women over 50 have a risk estimate of 1.158 IC 95% (1.039 - 1.292) with a p = 0.376 for the difference of means; In contrast to week 3 we can see a risk estimate of 1.023 95% CI (0.935 - 1.120). It should be noted that p = 0.548 in the difference in means is corroborated with ANOVA = 0.618, for week 4 the estimate of risk was not as marked as previous weeks reporting 0.985 95% CI (0.846-1.146) with a p = 0.527 and ANOVA of 0.845 finally for week 5 the risk estimate is seen in 1.143 IC 95% (1,003-1,103) with a p = 0.5 and ANOVA in 0.43, being able to conclude that age is perhaps not an important risk factor when starting concomitant treatment with cisplatin-radiotherapy.

Using the Friedman test with an alpha of 0.05 and a confidence interval of 95% comparing the weekly categories of acute renal failure according to the AKIN scale, a non-significant p value of 0.477 was obtained, so there is no increase in the incidence of acute renal failure in the studied population after a treatment with cisplatin at specified doses for 5 consecutive weeks under the described scheme.

With the Kruskal Wallis test measuring the difference of acute renal failure based on AKIN categories taking the population as a whole, a p-value of 0.599 was obtained, which is a non-significant result. Dividing in ages between under and over 50 years to compare the incidence of acute renal failure after treatment with weekly cisplatin taking into account the aging process in renal physiology was obtained a p-value of 0.118 for group 1 of under 50 years and a p-value of 0.6014 for group 2 over 50 years.

Separating into two age groups in older and under 50 years in the analyzes performed not significant changes are observed both in creatinine and in the weekly AKIN classification, but in a more detailed analysis it is appreciated that although the differences are not significant, in group 1 there is a greater amount of AKIN greater than 0 and in group 2 there is a greater difference between categories of AKIN per person, possibly due to the decrease in response to an injury due to physiological renal aging.

DISCUSSION

This retrospective study analysis attempts to analyze the relationship between acute renal failure and the administration of weekly cisplatin concurrent with radiotherapy, being able to appreciate that a good hydration is related to a small percentage of patients affected with acute renal failure during the treatment.

Faig et al, analyze the relationship between cisplatin at high doses and renal failure in head and neck tumors, reporting in their study to 6.1% of patients who develop renal failure, there are no similar studies in the cervix, however in our study it was observed that between 1.2% to 9.1% of patients develop a degree of renal failure during their treatment at low doses of cisplatin, this may be due to the susceptibility of patients, clinical stage IIIB that is accompanied by renal insufficiency, and gastrointestinal toxicity represented with diarrheic stools during radiotherapy sessions. (13)

The incidence of renal failure secondary to the use of cisplatin is well

established, although the type of relationship that exists with the administration of cisplatin, renal failure and age is not well defined, taking into account the decrease in physiological glomerular filtration rate of 50 years as well as the decrease of renal physiological protective mechanisms against renal injuries. There are few studies currently that evaluate the relationship between age and renal failure secondary to the use of cisplatin.

Wen, j. et al. In his article published in 2015, he concludes that there is a strong relationship between the decrease in the glomerular filtration rate, age and the administration of cisplatin. This study was conducted in patients with lung cancer and in mice with a larger population sample. In this study, neither the doses used of cisplatin nor concomitant administration of nephroprotective agents for cisplatin such as furosemide or mannitol are available, so it is unknown whether any of the regimens established for renal protection were used. In comparison with our study, we did not find a strong relationship between the administration of cisplatin and the decrease in glomerular filtration rate, probably due to the sample obtained, the use of nephroprotective agents for the administration of cisplatin and the fact that it is another type of cancer that may cause kidney damage through another pathophysiology. (14)

Hrushesky W. at the, in its publication of the year 1984, in an analysis of 43 patients receiving monthly cisplatin together with a protocol of hyperhydration without the use of diuretic evaluated renal function before and after treatment concluding that there is no decrease in renal function that is dependent on age secondary to the use of cisplatin, in this study we took into account the confounding factors that could bias the result. The study described and our study have a similar result with a population sample of almost a third although no nephroprotection measures have been used for renal failure secondary to the use of cisplatin, the similarity of results is probably due to high doses used in patients of both studies increased renal injury and exceeding the ability of the kidney to respond to an injury regardless of age. (15)

Appenroth D, et al. conducted a study in 1990 in mice evaluating whether kidney injury secondary to the use of cisplatin in the dependent age, concluding that younger mice having less renal damage in their macroscopic and microscopic renal structure probably due to a low differentiation of cell structure and transport in comparison with adult mice. This is one of the few studies that analyze renal changes microscopically and macroscopically, evaluating the differences between young patients and adults. In this study, structural changes and renal failure are analyzed using markers in mice, but they do not describe whether these changes are statistically significant and it is not known if the results can be extrapolated to humans. The difference in results may be due to a different renal physiology than the one that exceeds the objective of this study. (16)

Ali B, et al. in 2008, he conducted a study involving several ages, establishing kidney injury secondary to the use of cisplatin and its relationship with age, concluding that if there is a renal age-dependent injury secondary to the use of cisplatin regardless of the doses implemented in the scheme, suggesting future analyzes in animal models that compare pediatric, geriatric, as well as adult kidney injuries. This study has the same theoretical basis to the analysis implemented in our study but with different conclusions probably due to the tools used for the measurement of injury or renal failure as well as the models, determining otherwise injury or renal failure. (17)

Espandiari P, et al published in 2010 a study in mice relating age with renal failure in mice administered cisplatin at established doses but focused on pediatric ages. They conclude that kidney injury if it is dependent age secondary to the use of cisplatin and in postmortem microscopic studies in mice is related to the greater renal accumulation of cisplatin at different ages. In relation to our study that obtained a non-significant opposite result in relation to injury or renal failure age depended, the differences in results are probably due to the method of establishing renal injury or renal failure or animal models or in studies with humans. (18)

As can be seen, there are few studies in the medical literature that evaluate the age-dependent renal failure secondary to the use of cisplatin, probably because the physiological changes that the body has at different ages are generalized or underestimated. The few existing studies are mostly in animal models because of their easy access to post-mortem studies for microscopic analysis as well as the use of different ways of measuring kidney injury and perhaps in ways that do not make research more expensive.

CONCLUSION

These results are opposed to the physiological bases of decrease of glomerular filtration rate as well as to the results of some previously described publications with significant results in relation to age-related renal injury, it should be emphasized that in the protocols used in the patients of this study they used pre-established renal protection measures to reduce the likelihood of renal failure, so the results are probably due to the concomitant administration of these measures to reduce renal injury despite physiological changes with age.

In conclusion we can note that the age over 50 years, although it seems to have a greater tendency to present renal involvement during treatment for the time being at standard doses of treatment does not present a major effect, however, renal function must be constantly monitored and monitored.

Prospective longitudinal studies are needed with an identification of confounding factors to determine the real age dependence in relation to renal failure secondary to the administration of cisplatin.

LIMITATIONS OF THE STUDY

We believe it is convenient to indicate that as a study limitation this work was a retrospective observational study, it could not be recorded with a follow-up of creatinine values after the concomitance treatment, there are many losses in the system during the weeks of treatment in the same way we believe it is advisable to recommend with respect to implications for practice and future investigations, to evaluate RIFLE and AKIN scale, as well as urinary urination, electrolyte value to have more consistent data.

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