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Factors associated with chemotherapy toxicity in outpatients: a cohort study

Fatores associados à toxicidade à quimioterapia em pacientes ambulatoriais: um estudo de coorte

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ABSTRACT

Objectives: to identify the occurrence of toxicity associated with chemotherapy and predictors factors of hospitalization, delayed treatment, abandonment, treatment suspension or death. **Methods:** 126 patients with cancer were in a prospective cohort study, conducted between July/2012 and january/2013, they were interviewed before treatment and after completion of the 1st, 2nd and 3rd cycles, when clinical, demographic and laboratory data were collected. **Results:** 39,7% had toxicity grade ≥ 3. The latter led to more hospitalization, suspension, delayed treatment and death (p<0,05). Performance status 2 in cycles 1 (p<0,001) and 2 (p=0,025) were risk factors to the toxicity grade ≥ 3. When studied variables prior to first chemotherapy cycle, the body surface area < 1,69 m² was associated with the occurrence of toxicity grade ≥ 3 (p=0,023) and with anemia (p=0,044) and thrombocytopenia (p=0,006) of any grade. Creatinine clearance < 50mL/min was associated with anemia (p=0,032), BMI < 18,5kg/m² with thrombocytopenia (p=0,012), lymphocytes < 1500/mm³ to leukopenia (p=0,017), neutrophils < 3100/mm³ to neutropenia (p=0,002) and leukopenia (p<0,001), all of any toxicity grade. **Conclusion:** Approximately 40% of patients had toxicity grade ≥ 3, motivating more hospitalization, suspension, delayed treatment and death. Performance status 2 and body surface area < 1,69 m² were related toxicity grade ≥ 3.

Keywords: Drug-Related Side Effects and Adverse Reactions; Ambulatory Care; Antineoplastic Agents

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RESUMO

Objetivos: identificar a ocorrência de toxicidade associada à quimioterapia e fatores preditores de hospitalização, atraso no tratamento, abandono, suspensão do tratamento ou óbito. **Métodos:** 126 pacientes com câncer participaram de um estudo de coorte prospectivo, realizado entre julho/2012 e janeiro/2013, foram entrevistados antes do tratamento e após a conclusão do 1º, 2º e 3º ciclos, quando foram coletados dados clínicos, demográficos e laboratoriais. **Resultados:** 39,7% apresentaram grau de toxicidade ≥ 3. Este último levou a mais hospitalização, suspensão, atraso no tratamento e óbito (p<0,05). Performance status 2 nos ciclos 1 (p<0,001) e 2 (p=0,025) foram fatores de risco para o grau de toxicidade ≥ 3. Quanto às variáveis estudadas antes do primeiro ciclo de quimioterapia, a área de superfície corporal < 1,69 m^2 foi associada à ocorrência de grau de toxicidade ≥ 3 (p=0,023), anemia (p=0,044) e trombocitopenia (p=0,006) de qualquer grau. A depuração da creatinina < 50mL / min foi associada a anemia (p=0,032), IMC < 18,5kg /m^2 a trombocitopenia (p=0,012), linfócitos < 1500/mm^3 a leucopenia (p=0,017), neutrófilos < 3100 / mm^3 a neutropenia (p=0,002) e leucopenia (p<0,001), todas com qualquer grau de toxicidade. **Conclusão:** Aproximadamente 40% dos pacientes apresentaram grau de toxicidade ≥ 3, motivando mais hospitalização, suspensão, atraso no tratamento e óbito. O performance status 2 e a superfície corporal < 1,69 m^2 foram relacionados com grau de toxicidade ≥ 3.

Descritores: Efeitos colaterais e reações adversas relacionados a medicamentos; Assistência ambulatorial; Agentes Antineoplásicos

INTRODUCTION

Cancer is a public health issue, representing the second main cause of death in the world and brazilian populations. It is estimated, for Brazil, that between 2018 and 2019, there will be 600.000 new cases of cancer for each of those years.[1]

Many cancer patients need chemotherapy treatment. However, because of their low selectivity for tumor cells, citotoxic agents also affect healthy tissues, particularly those of rapid cell proliferation, like hair follicles, gastrointestinal tract and bone marrow. This tissues are often in cell division, becoming susceptible to action of citotoxic agents, that reach cells going through the cell division phase, causing adverse reactions that can be related to hematological and non-hematological factors.[2,3,4,5,6]

The National Cancer Institute (NCI) established criteria to assess the chemotherapy toxicity grade, ranging from 1 to 5: 1 being the mildest grade and 5 the most severe (death).7,8 Of these, the toxicity grade ≥ 3 cause greater concern, and can be associated to hospitalization, postponement, suspension of treatment and death.[4,9]

In Brazil, the studies on adverse reactions to chemotherapy did not consider the toxicity grade and were conducted in the southeast and south regions.[2,10,11,12] As a result of socioeconomic differences between brazilian regions, each region should be assessed separately.[13] The more precarious socioeconomic condition in the northeast may impact chemotherapy toxicity.

OBJECTIVES

This study aimed to identify the factors associated to toxicity resulting from adverse reactions to chemotherapy treatment and assess toxicity grade ≥ 3 as predictor of hospitalization, suspension and/or delayed treatment, and death of patients receiving chemotherapy in the outpatient oncology center of Instituto de Medicina Integral Prof. Fernando Figueira – IMIP, in order to optimize the management of possible adverse reactions.

METHODS

This is a prospective cohort study with patients receiving chemotherapy at the Oncology Outpatient Clinic of a School Hospital in Recife, capital of the state of Pernambuco, Brazil, called Instituto de Medicina Integral Professor Fernando Figueira (IMIP).

IMIP is a quaternary school hospital accredited by the Ministry of Health that develops teaching, research, community extension, assistance activities and works as a philanthropic entity. The IMIP Adult Oncology Service has been operating since 2004, currently attending about 30 to 40 new cases of chemotherapy per month, representing a public reference unit in clinical oncology in the northeast.

The study population consisted of 126 patients, aged 18 years or older who agreed to participate of the study. We excluded those with chemotherapy in the last year before the beginning of the study, altered cognition, concomitant diagnosis of more than one type of cancer, concomitant radiotherapy, active central nervous system (symptomatic) disease, performance status ≥ 3 (according to Eastern Cooperative Oncology Performance Status Rating) 14 or chemotherapy regimen with three cycles duration ≥ 6 months.

Between July/2012 and February/2013 the patients were interviewed through the application of questionnaires completed by the researcher (Appendices 1 and 2) before treatment and after the end of the first, second and third chemotherapy cycles. The study participants were asked about epidemiological, clinical profile and consequences of chemotherapy (hospitalization, suspension, delayed and death) and toxicity grade of the adverse reactions. For the last one, the Common Terminology Criteria for Adverse Events - CTCAE, version 4.0 / 2009 was used, in which the toxicity grade varies between 1 and 5, with 1 being the mildest and 5 being the most serious (death).[7]

An adverse reaction to chemotherapy was considered to be any harmful and undesirable reaction after administration of a drug, implying a causal relationship between the administration of the drug and the occurrence of the reaction, unintended harmful response, with a reasonable possibility of a causal relationship with the treatment.[15]

Toxicity grade ≥ 3 was assessed as an explanatory variable for the consequences of chemotherapy treatment and as a response variable to the clinical conditions of patients. The hematological factors (initial lymphocyte count, hemoglobin, neutrophils and platelets) and non hematological factors (body surface area, body mass index, performance status and creatinine clearance) prior to the first chemotherapy cycle were assessed as predictors of hematological or non-hematological adverse reactions with toxicity grade ≥ 3, as well as predictive factors of hematological adverse reactions of any grade and treatment consequences.

The data were analyzed with Stata 12.1. Cochran's Q test, Chi-square test and Fisher's exact test were used. Poisson regression was used in the multivariate analysis, with estimate of relative risks (RR), adjustment of the respective 95% confidence intervals (IC95%) and significance levels, and the variables that obtained a p value < 0.20 in univariate analysis participated in multivariate analysis. For all tests a significance level< 5% was considered.

The project was approved by the Research Ethics Committee of IMIP, under protocol 2983-12.

RESULTS

During data collection, 231 patients began chemotherapy treatment at the outpatient oncology center of IMIP as shown in figure 1. Number of patients excluded: 105, as follows: 55 patients received concomitant radiotherapy, five underwent chemotherapy in the previous year, two had active disease in the central nervous system, 11 were subjected to chemotherapy with three cycles duration ≥ 6 months, 32 were not captured before the first chemotherapy cycle (failure to capture). Thus, 126 patients were recruited.

All the recruited patients received the first chemotherapy cycle, 114 received up to the second cycle (six deaths and six treatment suspensions between the first and second cycles) and 104 received up to the third cycle (two deaths and eight treatment suspensions between the second and third cycles). Soon after the first cycle one patient died in a place outside the institution studied, and it has not been possible to obtain information about the occurrence of adverse reactions.

Most were female (71.4%), with brown skin color (52.8%), initial performance status 1 (57.9%) and staging III or IV (69.8%). The average age was 55 years. Most participants had completed only elementary school (46.7%), lived in the Recife's Metropolitan Region (68.3%) and had a per capita income of less than one minimum salary (64.4%), according to Table 1.

The most common cancer types were: breast (39%), lung (13%) and ovarian cancer (9.0%). The most commonly used chemotherapy treatments were: adriamycin + cyclophosphamide (30.2%) and carboplatin + paclitaxel (26.2%). Forty patients (31.7%) were receiving palliative treatment.

All 125 patients developed adverse events of any grade. The most common were: fatigue (85%), anemia (80%), alopecia (75%), dry mouth (72%), nausea (71%), anorexia (57%), constipation (52%), mucositis (47%), diarrhea (43%) and neutropenia (41%). The total number of patients who had some toxicity grade ≥ 3 was 50 (39.7%), neutropenia (16%), diarrhea (12%), anemia (8%) and nausea/vomiting (7%).

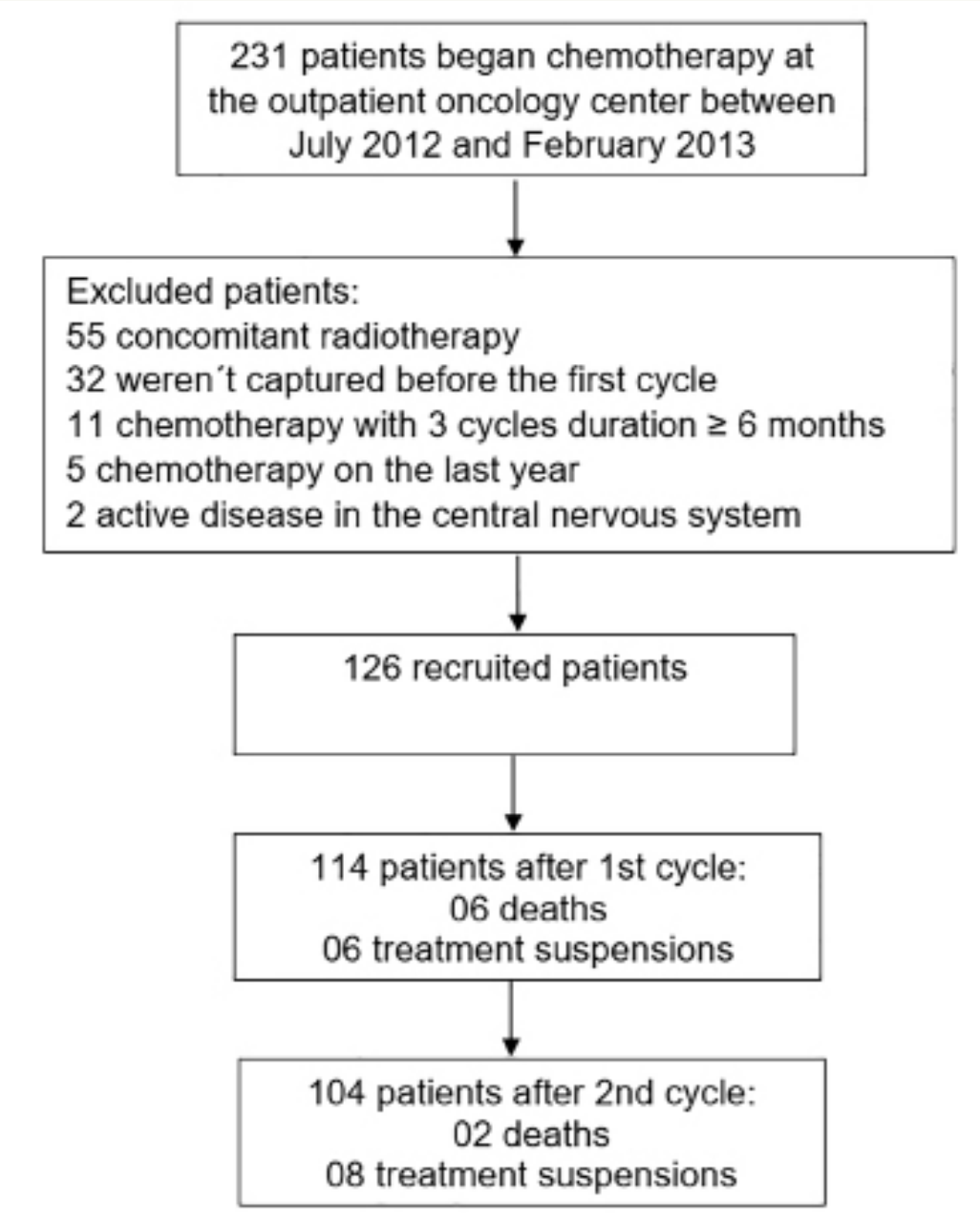

Figure 1. Flow chart for patient recruitment and follow-up.

There was no difference between the three cycles regarding the rate of occurrence of toxicity grade ≥ 3 (15.4% x 18.2% x 12.5%) (Cochran' test: $p<0.452$).

The incidence of consequences of adverse events among the patients who showed a toxicity grade ≥ 3 and those who did not were statistically significant for all the events: hospitalization (22% x 2.7%) ($p=0.001$), treatment suspension (16% x 2.7%) ($p=0.014$), delayed treatment (42% x 8%) ($p<0.001$) and death (10% x 0%) ($p=0.024$).

In univariate analyzes for cycles 1, 2 and 3 to study the relationship of toxicity grade ≥ 3 with sociodemographic variables (gender, race, origin, per capita income, schooling and age) and clinical variables (performance status, palliative or curative chemotherapy, cancer type and disease staging) the variables performance status 2 and cancer type presented $p<0.20$ in cycle 1 and cycle 2, following for multivariate analysis. In the table 2 are presented the final models of multivariate analysis for the toxicity grade

Table 1. Demographic and clinical characteristics of patients under chemotherapy treatment at the IMIP Oncology Service. Recife, PE, 2012/2013.

Variables	N (%)
Gender (N=126)	
Female	36 (28.6)
Male	90 (71.4)
Race (N=125)	
White	46 (36.8)
Black	13 (10.4)
Brown	66 (52.8)
Age (N=126)	
19 a 59	81 (64.3)
≥ 60	45 (35.7)
Origin (N=126)	
Recife's Metropolitan Region	86 (68.3)
Countryside	40 (31.7)
Schooling (N=122)	
Illiterate	10 (8.2)
Elementary school	57 (46.7)
High school	35 (28.7)
College/University	20 (16.4)
Per capita income (N=118)	
< 1 minimum salary	76 (64.4)
≥ 1 minimum salary	42 (35.6)
Basal Performance Status (N = 126)	
0	29 (23.0)
1	73 (57.9)
2	24 (19.0)
Disease Staging (N = 126)	
I	7 (5.6)
II	31 (24.6)
III	48 (38.1)
IV	40 (31.7)

* Variations of the sample in each category are due to a possible lack of information

Table 2. Final models of Poisson multivariate analysis for the relationship between occurrence of toxicity grade ≥ 3 due to adverse reactions in cycles 1 and 2.

Variable	RR (IC95%)	Value *p* - Wald
	Cycle 1	
Performance Status		0.002
0	1.19 (0.44 - 3.22)	
1	1.0	
2	3.34 (1.58 - 7.06)	
	Cycle 2	
Performance Status		0.019
0	1.0	
1	1.59 (0.61 - 4.16)	
2	3.76 (1.42 - 10.00)	

≥ 3 in cycles 1 and 2. In both performance status 2 remained a predictor of the toxicity grade ≥ 3.

In cycle 3, the variables disease staging IV and palliative chemotherapy were statistically significant in the univariate analysis (p=0.028 and p=0.007, respectively). However, these variables were not be able to perform a multivariate analysis for cycle 3, because all participants in stage IV received palliative chemotherapy, and this treatment was not applied to stages I,II and III. So these two variables could not be predictors of toxicity grade ≥ 3.

The possibility that some factors prior to beginning of chemotherapy were associated to consequences of adverse reactions was assessed, and the only statistically significant association found was between creatinine clearance < 50mL/min and the occurrence of chemotherapy suspension (p=0.019).

Among the factors associated to hematological or non hematological adverse reactions with toxicity grade ≥ 3 prior to chemotherapy treatment, the factors that showed statistical significance were body surface area < 1.69m² (p=0.024) and platelet < 150.000/mm³ (p=0.007). When any toxicity grade was considered, statistical significance was observed with body surface area < 1.69m² (p=0.044), creatinine clearance < 50mL/min (p=0.032) and initial lymphocyte count < 1500/mm³ (p=0.046) associated to anemia; BMI < 18.5kg/m² (p=0.012) and body surface area < 1.69m² (p=0.006) associated to thrombocytopenia; initial neutrophil count < 3100/mm³ (p=0.002) associated to neutropenia and leukopenia (p<0.001); platelet < 150.000/mm³ (p=0.006) and lymphocyte < 1500/mm³ (p=0.017) counts associated to leukopenia.

On the other hand, when the factors associated only to hematological adverse reactions with toxicity grade ≥ 3 were assessed, initial hemoglobin < 10g/dL (p<0.001) was associated to anemia grade > = 3; initial neutrophil count < 3100/mm³ (p=0.007), as shown in table 3. and platelets < 150.000/mm³ (p=0.028) were associated to neutropenia grade > = 3.

Table 3. Univariate analysis of the factors associated to hematological or non hematological adverse reactions with toxicity grade ≥ 3 prior to chemotherapy treatment.

Variable	Sample N 123*	Toxicity Grade ≥ 3 N (%)	RR (IC95%)	Value *p***
Nutritional status				0.894
Malnutrition	7	3 (42.9)	1.10 (0.44 - 2.73)	
Eutrophy	46	20 (43.5)	1.11 (0.71 - 1.75)	
Overweight/obesity	64	25 (39.1)	1.0	
Body Surface				0.024
< 1.69m²	65	33 (50.8)	1.76 (1.08 - 2.88)	
> = 1.69m²	52	15 (28.8)	1.0	
Hemoglobin				0.228
< 10g/dL	13	7 (53.8)	1.41 (0.81 - 2.47)	
> = 10g/dL	110	42 (38.2)	1.0	
Neutrophil count				0.529
< 3100/mm³	27	12 (44.4)	1.17 (0.71 - 1.93)	
> = 3100/mm³	95	36 (37.9)	1.0	
Platelet count				.
< 150.000/mm³	2	2 (100.0)	2.57 (2.06 - 3.22)	0.007
≥ 150.000/mm³	121	47 (38.8)	1.0	
Creatinine Clearance				0.263
< 50mL/min	9	5 (55.6)	1.44 (0.76 - 2.72)	
> = 50mL/min	101	39 (38.6)	1.0	

* Variations of the sample in each category are due to a possible lack of information
** Wald Test

DISCUSSION

In contrast with other studies,2,16 all patients experienced at least one adverse reaction of any grade. This divergence can be explained by the fact that this study involved the analysis of a wider range of adverse events.

Regardless of the toxicity grade, the frequency of nausea,[16] vomiting, anorexia, dyspepsia, anxiety,2 mucositis,[17] extravasation,[18] anemia, fatigue, diarrhea, neuropathy and allergic reaction19 was similar to the literature, which did not occur with dry mouth,[13] neutropenia and thrombocytopenia[20], though.

The frequency of toxicity grade ≥ 3 was 39.7%, unlike other studies21,22 that obtained frequencies of 46.3% to 65.6% and 79%. This can be explained by the smaller number of cycles assessed in the current study and because one of the comparative studies involved only patients with advanced (IIIB and IV) lung cancer and the another one was a meta-analysis with advanced colorectal cancer.[21,22]

The adverse reactions with toxicity grade ≥ 3, such as anemia, thrombocytopenia, febrile neutropenia, nausea, vomiting, diarrhea, constipation, anorexia, allergic reactions and fatigue were similar to those reported in the studies. Neutropenia (16% x 49.7% to 63%) and leukopenia (8% x 34.2%) were divergent, possibly because of the lower number of cycles assessed in the current study.[19,21,23,24,25]

Regarding the consequences of adverse events, the rate of occurrence of death (3.2%) was similar to the findings of other studies that ranged between 1% and 4%[23]. The rate of delayed treatment was 21.4%, lower than the date reported in the literature (31% to 86%).4,12 One of the studies used for this last comparison was based on concomitant chemotherapy and radiotherapy, providing greater toxicity to the treatment, and the other study concerned only patients > 65 years.[4,12] Regarding treatment suspension, the rate was 7.9%, in contrast with other studies (15% and 32.1%), probably due to the lower number of cycles investigated in this study and the advanced age of patients in the comparative studies.[2,23] The rate of hospitalization was 10.3%, lower than the one obtained by Hurria and collaborators (23%), where patients were aged > 65 years.[4]

Significantly higher significant rates of hospitalization, suspension or delayed treatment and death were observed among the patients who had a toxicity grade ≥ 3. Analysis of other studies was not possible because they don't compare the consequences of adverse reactions with toxicity grade.[2,4,12,21,23]

Assessment of clinical variables showed that only PS 2 in cycle 1 and in cycle 2 showed a statistically significant association with toxicity grade ≥ 3. Although no studies assessing each chemotherapy cycle were found, it is expect that PS, because it quantifies patient functionality has impact on adverse reactions.[7]

Among the variables prior to chemotherapy associated to adverse reactions with toxicity grade ≥ 3, the only one with statistical significance was body surface area. Alvarez-Cabellos and collaborators obtained a significant association between low body surface area and the incidence of hematological and non hematological toxicity grade ≥ 3.[25] Nowadays the use of body surface area to calculate the dose of chemotherapy has been questioned because it is not a good indicator of liver and kidney function, that are important predictors of chemotherapy toxicity. There is growing literature to suggest that lean body mass or fat free mass (FFM), which is mainly composed of skeletal muscle and metabolic tissues such as liver and kidney, may be a better basis for drug dosages in cancer patients. So variability in body composition of cancer patients may be a source of disparities in the metabolism of cytotoxic agents, for example sarcopenia, that is a degenerative loss of skeletal muscle mass, is important because it increases the risk of toxicity to many chemotherapy drugs.[26]

In the present study, the factors associated to hematological adverse reactions of any grade were body surface area creatinine clearance, BMI, initial neutrophil, platelet and lymphocyte counts, which is corroborated by other studies.[4,27] The pretreatment neutrophil < 3100/mm^3 and lymphocyte < 1500/mm3 counts were predictive factors for neutropenia of any grade, creatinine clearance < 50mL/min was associated with increased risk of neutropenia, and < 80mL/min was associated with increased risk of toxicity regardless of the grade.[3,5,27]

In this study, the factors associated to hematological adverse reactions with grade ≥ 3 were hemoglobin, the count of neutrophils and platelets before the first cycle, similar to other studies, where there was association with hemoglobin, platelet count, lymphocyte count, performance status and creatinine clearance.[2,28]

The limitations of this study are: reduced time (three months) of patient monitoring, failure to capture some eligible patients, limited total number of participants and small proportion of elderly in the sample, multiplicity of chemotherapy treatments used and loss of follow-up of 22 patients (17.5%) due to death or chemotherapy suspension. As positive points of the study we can cite: few toxicity studies evaluate cycles separately and their impact on outcome.

CONCLUSIONS

The adverse reactions with toxicity grade ≥ 3 were related to complications in chemotherapy treatment, such as hospitalization, treatment suspension, delayed treatment and death.

The performance status 2 had a statistically significant association with the occurrence of toxicity grade ≥ 3. Basal laboratory tests, body mass index and body surface area are factors that may predict adverse reactions, regardless of the toxicity grade and chemotherapy cycle. In the future, we should confirm these data and try to improve performance status and nutritional status of patients in order to improve their chemotherapy tolerance.

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APPENDICE 1

DATA COLLECTION FORM IN SUBJECT CAPTATION

FORM NUMBER: _____ DATE:_____ TELEPHONE: _____

NAME:_____ REGISTRATION:_____

Schooling: 1. Illiterate 2. Elementary school 3. High school 4.University

Number of people living in the same household

Total family income _____

Per capita income _____

Origin: 1. Metropolitan Region of Recife 2. Countryside 3. Other_____

WEIGHT_____HEIGHT_____

BODY MASS INDEX_____BODY SURFACE_____

PERFORMANCE STATUS

1 ( ) Totally asymptomatic = 0

2 ( ) Non-disabling mild symptoms = 1

3 ( ) Symptoms that incapacitate, but are capable of self-care = 2

DATE OF ENTRY INTO STUDY: _____

DIAGNOSIS (underlying disease):

1 ( ) head and neck	8 ( ) pancreas	15 ( ) kidney
2 ( ) esophagus	9 ( ) lung	16 ( ) bladder
3 ( ) stomach	10 ( ) melanoma	17 ( ) Hodgkin's lymphoma
4 ( ) colon	11 ( ) breast	18 ( ) Non-Hodgkin's lymphoma
5 ( ) rectum	12 ( ) cervix	19 ( ) prostate
6 ( ) anal canal	13 ( ) ovary	20. Other.What?
7 ( ) biliary tract	14 ( ) endometrium	

STAGING OF DISEASE:

1. ( ) I 2. ( ) II 3. ( ) III 4. ( ) IV

WHAT IS THE CHEMOTHERAPY REGIMEN IN EFFECT?

PURPOSE OF THE TREATMENT: 1. ( ) Curative 2. ( ) Palliative

LABORATORY EXAMS

HEMOGLOBIN_____TOTAL LEUKOCYTES_____

NEUTROPHILS_____ LYMPHOCYTES_____

CREATININE_____ PLATELETS_____

CREATININE CLEARANCE_____

APPENDICE 2

FORM USED AFTER EACH CHEMOTHERAPY CYCLE (CYCLES 1, 2 AND 3)

FORM NUMBER:_____ DATE:_____

NAME:_____ REGISTRATION: _____

CYCLE_____ CYCLE DATE_____ WEIGHT _____

PERFORMANCE STATUS

1 ( ) Totally asymptomatic = 0

2 ( ) Non-disabling mild symptoms = 1

3 ( ) Symptoms that incapacitate, but are capable of self-care = 2

LABORATORY EXAMS

HEMOGLOBIN_____ TOTAL LEUKOCYTES_____

NEUTROPHILS_____ LYMPHOCYTES_____

CREATININE_____ PLATELETS_____

WHAT IS THE ADVERSE EFFECT PRESENTED AND ITS TOXICITY GRADE?

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea				
Oral Mucositis				
Nausea				
Vomiting				
Dyspepsia				
Dry mouth				
Anorexia				
Constipation				
Fatigue				
Sensory neuropathy				
Anxiety				
Allergic reaction				
Anemia				
Thrombocytopenia				
Neutropenia				
Febrile neutropenia				
Leukopenia				
Acute renal insufficiency				
Hand-foot Syndrome				
Alopecia				
Extravasation				

HAVE SUSPENSION OF TREATMENT DUE TO ADVERSE REACTION(S)?

YES ( ) NO ( )

IF YES, WHICH SYMPTOM (S) WAS RESPONSIBLE(IS) FOR SUSPENSION? _____

HAVE DELAYING OF TREATMENT DUE TO ADVERSE REACTION(S)?

YES ( ) NO ( )

IF YES, WHICH SYMPTOM(S) WAS RESPONSIBLE(IS) FOR DELAYING? _____

HAVE HOSPITALIZATION DUE TO ADVERSE REACTION(S)?

YES ( ) NO ( )

IF YES, WHICH SYMPTOM(S) WAS RESPONSIBLE(IS) FOR HOSPITALIZATION? _____

HAVE ABANDONMENT OF TREATMENT DUE TO ADVERSE REACTION(S)?

YES ( ) NO ( )

IF YES, WHICH SYMPTOM(S) WAS RESPONSIBLE(IS) FOR ABANDONMENT?_____

HAVE DEATH DUE TO ADVERSE REACTION(S)?

YES ( ) NO ( )

IF YES, WHICH SYMPTOM(S) WAS RESPONSIBLE(IS) FOR DEATH?_____