



THE INFLUENCE OF CHEMOTHERAPIC AGENTS AND THEIR ACCESSORIES ON ORAL MANIFESTATIONS OF ACUTE LYMPHOID LEUKEMIC CHILDREN

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ABSTRACT

Aim: To evaluate the influence of chemotherapy agents and their accessories on oral manifestations of children who have acute lymphoid leukemia.

Material and Methods: After the stipulated period for the research, the total sample reached was of 68 children. Nevertheless, only 46 children had continued for the second period. Children from 2 to 12 years of age who had been diagnosed with ALL – and would be submitted to treatment at Ophir Loyola Hospital, in Belém, State of Pará – had been included in the research. The first evaluation has been held before the chemotherapy treatment and had offered anamnesis and clinical exams. The second evaluation has been held in 10 to 15 days after the beginning of chemotherapy treatment and has offered a new clinical exam and annotations of the drugs which had been utilized during the chemotherapy.

Results: From the drugs given at Ophir Loyola Hospital, it has been observed that 14 to 24mg (83%), vincristine 0,6mg to 1 g (80%), ARA-C 20mg to 1600mg (74%), cardioxane 13mg to 340mg (65%), methotrexate 12mg to 2400mg (63%), cyclophosphamide 104mg to 1540mg (59%), asparaginase 50UI to 9600UI (57%) and mesna 75mg to 510mg (54%) have been used the most. No drug has presented statistic at 5% level in Fisher exact test, when crossing with the presence of the main mouth manifestations: mucositis, xerostomia, toothache, and dysphagia.

Conclusions: In the face of the results, it can be concluded that there has been no influence of the chemotherapy agents and their accessories in the oral manifestations of acute lymphoid leukemic children; nevertheless, these patients may present any kind of lesion on the mouth cavity during or after the beginning of chemotherapy. The dental surgeon needs to recognize the oral manifestations and intervene on the buccal health of the ALL patients, contributing and helping with his/her treatment.

KEYWORDS: chemotherapeutic, oral manifestations, children

<http://dx.doi.org/10.19177/jrd.v4e62017141-144>

INTRODUCTION

Acute lymphoid leukemia (ALL) affects around 80% of leukemia, and it occurs in most cases with children¹. ALL is a result of an excessive and uncontrolled production of blasts of the lymphoid kind, making the normal production of red and white blood corpuscles, as well as blood platelets. The chances of survival had increased with the advance in the types of anti-neoplastic treatment^{2,3}.

The chemotherapy drugs act systematically on the cell level, specifically on the cells with a cell division process, interfering with its growth and division¹. During the anti-neoplastic treatment, the buccal lesions become even more intense, for the chemotherapy treatment acts on little-differentiated cells, or with a high metabolism rate, which affects beyond the blastic and normal organism cells³.

Having this exposed, our goal is to evaluate the influence of chemotherapy agents and their accessories on the oral manifestations of children affected by acute lymphoid leukemia.

MATERIAL AND METHODS

This research has been submitted to the evaluation of the Ethics Committee of Research with Human Beings, through the Cruzeiro do Sul University Ethics Committee, which has approved it with protocol number CE/UCS-005/2014.

The legal tutors of the selected children had been clarified and informed about the research; the ones who, after reading the Informed Consent Form-ICF – had agreed with the participation of their child, had signed the paper.

The final sample of this study has been constituted of 46 children who

had been enrolled/attended at Ophir Loyola Hospital (OLH), a reference to the cancer treatment of the public service in the State of Pará. Convenience sample has been adopted, one cancer in children and teenagers is a rare condition, which corresponds to about 3% of all malign tumors in most of the populations (OMS, 1997).

The criteria of inclusion that has been used was the inclusion of children affected with acute lymphoid leukemia – ALL, who had been submitted to anti-neoplastic treatment, with chemotherapy from ages 2 to 12 years old; both genders, independently of the skin color or social and economic conditions, all residents of the State of Pará.

In order to diminish the variability of inter-examiner diagnosis and higher the reliability of the data identified, a training and calibration have been held previously at the beginning of the exams. The agreement of inter-examiner diagnosis was of 0.78, which has been considered a good rate.

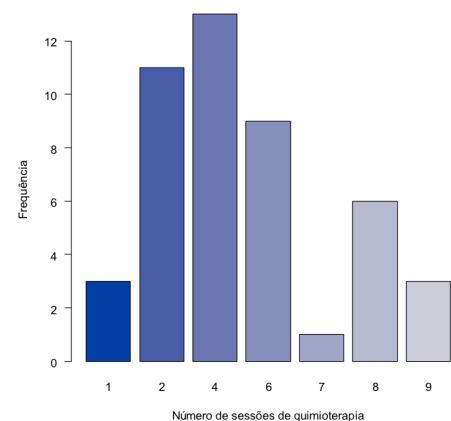
The data collection had been performed in two stages: The first one after the receiving of the cancer diagnosis and before the anti-neoplastic treatment and it has been done with anamnesis and clinical exam. In the second stage, approximately 10 to 15 days after the beginning of the anti-neoplastic treatment, a new clinical exam has been done and there have been annotations of drugs that had been used during chemotherapy.

RESULTS

All examined children were doing the first cycle of chemotherapy. Nevertheless, the frequency of a number of sessions done by the second stage of the research has been evaluated, as figure 1 shows.

The number of typical chemotherapy sessions (trend) was of four, which is also the average of this distribution, having a minimum of one session and a maximum of nine. The interquartile interval varies from two to six sessions.

Figure 1. Number of chemotherapy sessions of children from the sample.

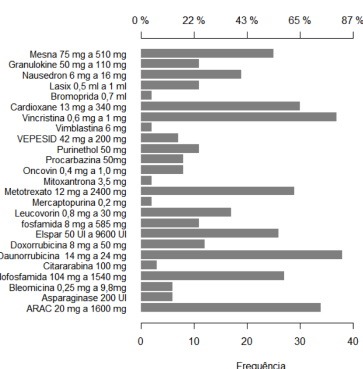


Chemotherapy is a treatment that uses medication to destroy sick cells. The drugs given at OLH are the ones that follow on figure 2. It has been observed that daunorubicin 14 to 24mg (83%), vincristine 0.6mg to 1 g (80%), ARA-C 20mg to 1600mg (74%), cardioxane 13mg to 340mg (65%), methotrexate 12mg to 2400mg (63%), cyclophosphamide 104mg to 1540mg (59%), asparaginase 50UI to 9600UI (57%) and mesna 75mg to 510mg (54%) were the most used ones. It is important to note that the drugs cardioxane and mesna are accessories to the chemotherapy treatment.

Table 1 summarizes the analysis of the possible influence of drugs on buccal alterations. The 32 contingency tables are disposed on the table with drugs in the columns and the types of buccal alterations in the group of lines. The lines named “%” are the ones that present percentages of each factor to its respective column. The lines named “X²” present the chi-square statistic calculus

for each table of contingency. The lines nominated “p-valor” (p-value) present the p-value taking into consideration the number of degrees of freedom of the corresponding contingency.

Figure 2. Drugs used for children’s treatment. The six superior bars nominate the accessory drugs.



Because Fisher’s exact test had been used, the chi-square statistic value has been left blank, for, in this case, the p-value is calculated without this statistic.

None of the contingency tables above present statistical significance on

the level of 5%, or, explaining in another way, in the level of 5% in none of the contingency tables above the independency null hypothesis can be discarded among the category variables of each crossing of each table.

DISCUSSION

Chemotherapy is usually composed by liquid medication that is mixed into the saline solution and injected into the patient. Each session lasts about one hour. The session numbers vary according to the patient, but they are generally an average of six to eight applications. The time interval between them is also variable, but it is of usually of 21 days (THOMAZ et al., 2013). In this research, the average of sessions has been of 4.63. Nevertheless, 9 patients had made 6 sessions, 1 had made 7 sessions and 6 had made 8 sessions. Subramaniam, Babu & Nagarathna (2008) and Torres, et al. (2010) had evaluated the oral manifestations in

children with ALL during the chemotherapy process. They had performed intraoral exams after the fourth and the third sessions, respectively.

The possible collateral effects of chemotherapy are countless. Morais et al. (2014) had identified that among the most uncomfortable symptoms according to the children in treatment, there are: nausea and vomiting, weight gain, pain, hypersensitiveness reaction, fatigue, and fever. These symptoms interfere directly in their daily lives, causing them to have the state of well-being diminished and, consequently, a worsening of the life quality.

For many times this is the moment when the child or the teenager notices himself/herself as truly sick, which is aggravated by the restricted periods of hospitalization, as well as home stays. This makes them experiment the process in a more difficult way.

Table 1. Frequency of the different buccal alterations according to drugs used in chemotherapy.

Alteração	Variável	Casos	Mesna		Cardioxane		Vincristina		Metotrexato		Daunorubicina		Ciclofosfamida		Elspar		ARAC	
			S	N	S	N	S	N	S	N	S	N	S	N	S	N	S	N
Mucosite	Total, n	46	25	21	30	16	37	9	29	17	38	8	27	19	26	20	34	12
	Sim	16	9	7	10	6	12	4	9	7	14	2	11	5	10	6	11	5
	Não	30	16	14	20	10	25	5	20	10	24	6	16	14	16	14	23	7
	%		36	33	33	38	32	44	31	41	37	25	41	26	38	30	32	42
	X ²		0,036		0,080		-		0,486		-		1,023		0,357		-	
	p-valor		0,850		1,000		0,497¶		0,486		0,523¶		0,312		0,550		0,818¶	
Xerostomi	Sim	12	8	4	8	4	9	3	6	6	11	1	9	3	5	7	7	5
	Não	34	17	17	12	22	28	6	23	11	27	7	18	16	21	13	27	7
	%		32	19	27	25	24	33	21	35	29	12	33	16	19	35	21	42
	X ²		0,993		-		-		-		-		-		0,755		-	
	p-valor		0,319		1,000¶		0,898¶		0,459¶		0,603¶		0,320¶		0,385		0,153¶	
Odontoalgi	Sim	10	5	5	8	2	7	3	7	3	8	2	4	6	7	3	8	2
	Não	36	20	16	22	14	30	6	22	14	30	6	23	13	3	17	26	10
	%		20	24	27	12	19	33	24	18	21	25	15	32	27	15	24	17
	X ²		-		-		-		-		-		-		-		-	
	p-valor		0,755¶		0,463¶		0,347¶		0,885¶		0,806¶		0,320¶		0,541¶		0,620¶	
Disfagia	Sim	10	5	5	7	3	7	3	7	3	7	3	4	6	6	4	8	2
	Não	36	20	16	23	13	30	6	22	14	31	5	23	13	20	16	26	10
	%		20	24	23	19	19	33	24	18	18	38	15	32	23	20	24	17
	X ²		-		-		-		-		-		-		-		-	
	p-valor		0,755¶		1,000¶		0,624¶		0,885¶		0,473¶		0,320¶		1,000¶		0,930¶	

When searching for literature about the drugs used during the chemotherapy treatment for ALL, it could have been noticed the lack of agreement, as well as the scarcity about the subject. Pinto et al. (2006) had detected that the protocol used for the treatment of acute leukemia has been proposed by the Brazilian Society of Pediatric Oncology, and methotrexate is one of the most used drugs in this therapy. Chlorhexidine gluconate 0.12% has been administered for 10 consecutive days, after each infusion of methotrexate during chemotherapy. Subramaniam et al. (2008) had observed that the most used drugs were daunorubicin 30mg, vincristine 1.4 mg, L-asparaginase, methotrexate 12 mg. Torres et al (2010) had identified doxorubicin, vincristine, prednisone, L-asparaginase and methotrexate as the most used drugs. Pelse Mielnik (2012) only state that the Berlin-Frankfurt-Münster Protocol has been used. Mendonça et al. (2012) had only also stated that the protocol that has been used was the one proposed by Brazilian Society of Pediatric Oncology.

Chemotherapy treatment may be directly toxic and affect the oral mucosae by the systemic circulation. Besides that, for many times the saliva secretion of the used drugs occurs, which results in medication exposition in the oral cavity. The analysis has been made between the buccal alterations incidence and the used drugs, and the correlation has not been statistically significant. Corroborating with our findings, Pinto et al. (2006), Subramaniam et al. (2008), Torres et al. (2010), Pels & Mielnik (2012), Mendonça et al. (2012) had stated that the use of the medicine combination on chemotherapy cannot be directly correlated with the oral manifestations that are present in the individual.

However, it is important to expose the study of Hsieh et al. (2011), in which a research has been developed to evaluate the effect of anti-neoplastic therapy on the dental development and on the salivary function in receptors of anti-neoplastic therapy during the childhood. They have concluded that the children and the teenagers who had received high doses of cyclophosphamide had a higher risk of developing dental disorders.

CONCLUSIONS

In the face of the results, it has been concluded that there has not been an influence of the chemotherapy agents and of their accessories on the oral manifestations of acute lymphoid leukemic children. However, those patients may present some lesion on the oral cavity during or after the beginning of chemotherapy treatment. The dentist surgeon needs to recognize the oral manifestations and intervene on the ALL patient's buccal health, contributing and helping with his/her treatment.

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