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FATORES PROGNÓSTICOS NO LINFOMA DE HODGKIN PEDIÁTRICO NO ESTADO DO PARANÁ – BRASIL

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Prognostic factors in pediatric Hodgkin's Lymphoma in Paraná state - Brazil

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Summary:

While the 5 year global survival rates for Hodgkin Lymphoma patients are beyond 93%, the toxicity of the treatment is a major problem. We performed a study that aims to identify prognostic factors at diagnosis that could suggest more or less aggressive treatment protocols. In this population, the 5 years overall survival rate was 93,8%, while the 5 years event-free survival was 86,7%. Advanced stages, involvement of more than one site at diagnosis, extranodal disease and the delay on sending the patient for the specialist were identified as prognostic factors.

Introduction:

Lymphomas are the third most incident cancer in American children (14,6%), and the second in Brazil (15,5%)[1]. Hodgkin's lymphoma (HL) is the sixth diagnose in all pediatric cancers. While the 5 year global survival rates are beyond 93%[2], the toxicity of treatment is a major problem.

Children treated for HL have 10 to 80 times higher risk to develop leukemia or mielodysplasia than the non-treated population[3,4,5], and an important number of patients die from cardiovascular complications[6]. Infertility, solid tumors, failure to thrive, thyroid and cardiac failure are important late complications of the tratment[3,5].

Methods:

We performed a review of all pediatric HL cases treated from 1982 to 2005 in 2 major pediatric cancer treatment centers in Curitiba, Brazil (Clinicas Hospital of Federal University of Paraná and Erasto Gaertner Hospital). The study aims to identify prognostic factors at diagnosis that could suggest more or less aggressive treatment protocols. Patients still in treatment or previously treated in another service were excluded. For prognostic factors analysis, 21 patients were excluded because their treatment finished less than 5 years ago. The data was analyzed by Epi-info software, and the research was approved by the Clinicas Hospital Human Research Ethics Committee.

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No interest conflicts were reported.

Results:

Of the 169 patients initially analyzed, 49 were excluded (28%). Previous treatment in another service was responsible for 45% of the exclusions. The background data of the participants is shown in Table 1.

Chemotherapy was administered in 96% of the patients, 34% with ABDV protocol, 20% OPPA and 11% MOPP. Radiotherapy was associated in 86,6% of the cases, 75% with enlarged field. The 5 years overall survival rate (OS) was 93,8% (Fig 1), while the 5 years event-free survival (EFS) was 86,7% (Fig 2).

Univariable analysis of factors predicting treatment failure is shown in Table 2. Age, sex, histopathology, presence of B symptoms, bulky mediastinal disease or any bulky disease and hemoglobin level at diagnosis couldn't statistically predict local failure. Treatment-related factors, including the type of chemotherapy and association of radiotherapy, did not predict for local treatment failure as well. The risk of local failure was three-fold higher for patients with III and IV Ann Harbor stages (23,3%) than for those with stages I and II (7,1%; P = .006; Fig 3). Thirteen of 67 patients with involvement of more than 1 site at diagnosis experienced relapse in 5 years (19,4%), six-fold higher risk than those with just 1 site involved (3,1%. P = .03; Fig 4). The sending for a specialist by the local pediatrician was delayed more than 12 months for 13 patients. The relapse in this group was 3-fold higher (30,8%) compared with those who were immediately sent (11,6%; P = .03).

Multivariable analysis of prognostic factors that independently predicted local failure revealed that extranodal disease (p=0,0189) and involvement of more than 1 site at diagnosis (p=0,0488) were significant predictors of local failure.

Discussion:

The data in our study confirmed a developing country pattern of HL (epidemiological type 1), characterized by a high incidence of mixed cellularity histological subtype. Median age was slightly lower than in developed countries, although higher than developing countries reports[7].

Treatment protocol in children with HL involves the combined use of multidrug chemotherapy and associated radiotherapy. The OS and EFS in 5 years were 93,8% and 86,7%, respectively. In Turkey, Oguz et al reported 96,2% and 90,7% rates (respectively) in a small population analysis[7], while in U.S.A, Krasin et al reported 93,1% and 83,8% rates (respectively) in a 195 patients cohort[2]. Despite the high proportion of treatment failures among patients who experienced disease recurrence, the overall incidence of treatment failure was low.

The goals of the treatment continue to be to reduce therapy and toxicity for patients with favorable presentation of the disease. The identification of prognostic factors at diagnosis and the adaptation of therapy according to the disease's response to initial treatment is the standard of care[2]. In pediatric patients, Smith et al.[8] revealed that male gender, stage IIB, IIIB,

or IV disease, bulky mediastinal disease, hemoglobin <11.0 g/dl and WBC = 11.5 x $10^3/mm^3$ were factors that independently predict inferior EFS and OS rates. For Oguz et al.[7], pretreatment factors influencing the 5-year EFS which were determined by univariable analysis were stage, number of involved nodal sites, extranodal disease, and initial hemoglobin level <11 g/dl. In developed countries, the St. Jude group reported that any bulky disease, bulky mediastinal disease, hemoglobin < 11mg/dL and Erythrocyte sedimentation rate > 50 predict local treatment failure in univariable analisys[2].

In our study Ann Harbor stages III and IV, number of involved nodal sites at diagnosis and late specialist evaluation predict treatment failure in univariable analysis. Ann–Arbor classification describing the anatomic distribution and thus dissemination of tumor cells has been demonstrated to be of prognostic relevance for EFS in several studies. Furthermore, there is consensus about the pronounced prognostic impact of dissemination of HD according to Ann Arbor classification[7]. Stages III and IV are related to more nodal sites involved at diagnosis (r=0,448; p<0,0001; Pearson's relation).

In multivariable analysis, the number of involved nodal sites and the presence of extranodal disease independently predict treatment failure. Both are related to extension of disease, and are found to be prognostic factors in literature[2,7,8,9,10].

However, age, sex, histopathology, presence of B symptoms, bulky mediastinal disease or any bulky disease and hemoglobin level were not identified as prognostic factors. This suggests that the success of the adaptation of the treatment protocols annuls the worse prognosis of the variables[11].

The median time from the first symptoms and the specialist evaluation was 7.4 months. This data suggests low suspicion by the local pediatricians, since the average time to evaluation in our centers is less than 1 week. As university centers, we are working with local public health system to encourage local physicians to promptly refer suspicious cases to an oncology/hematology center.

Different of other studies, the delay on sending the patient to an specialist evaluation proved to be an important prognostic factor, that can be fixed with concerted educational actions.

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FIG. 1 – 5 YEAR OVERALL SURVIVAL

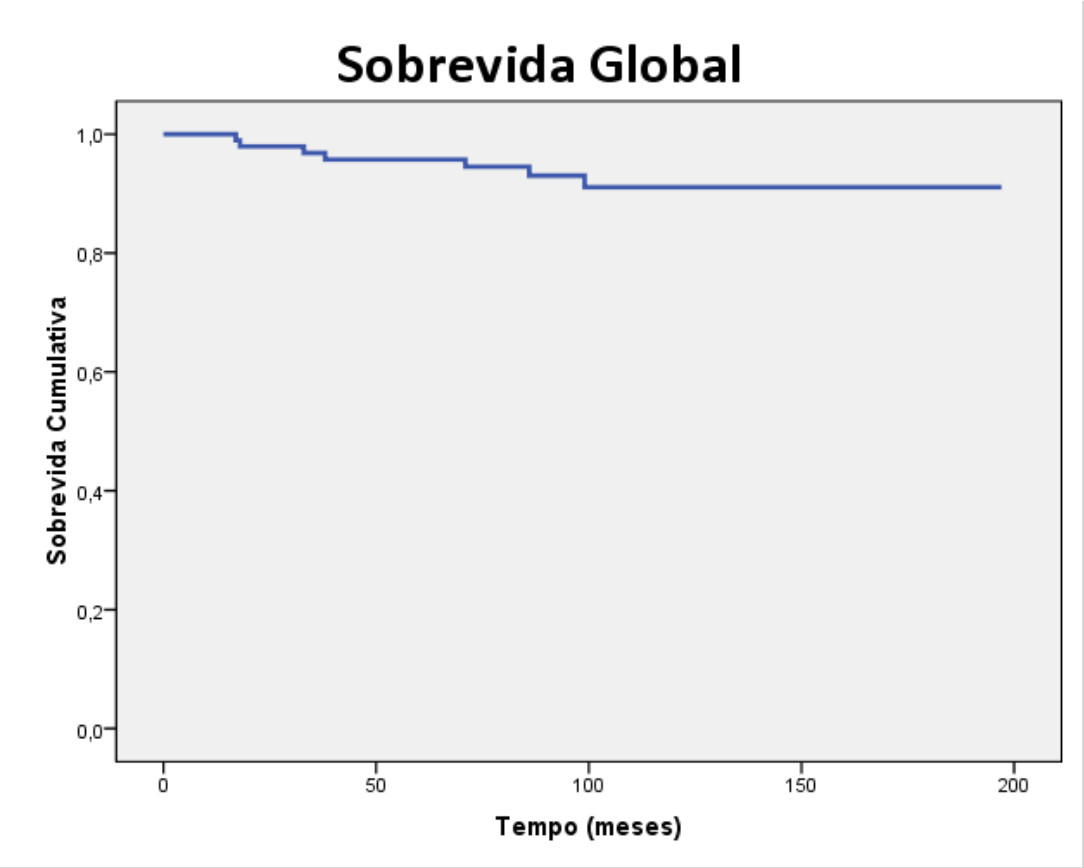

FIG. 2 – 5 YEAR EVENT-FREE SURVIVAL

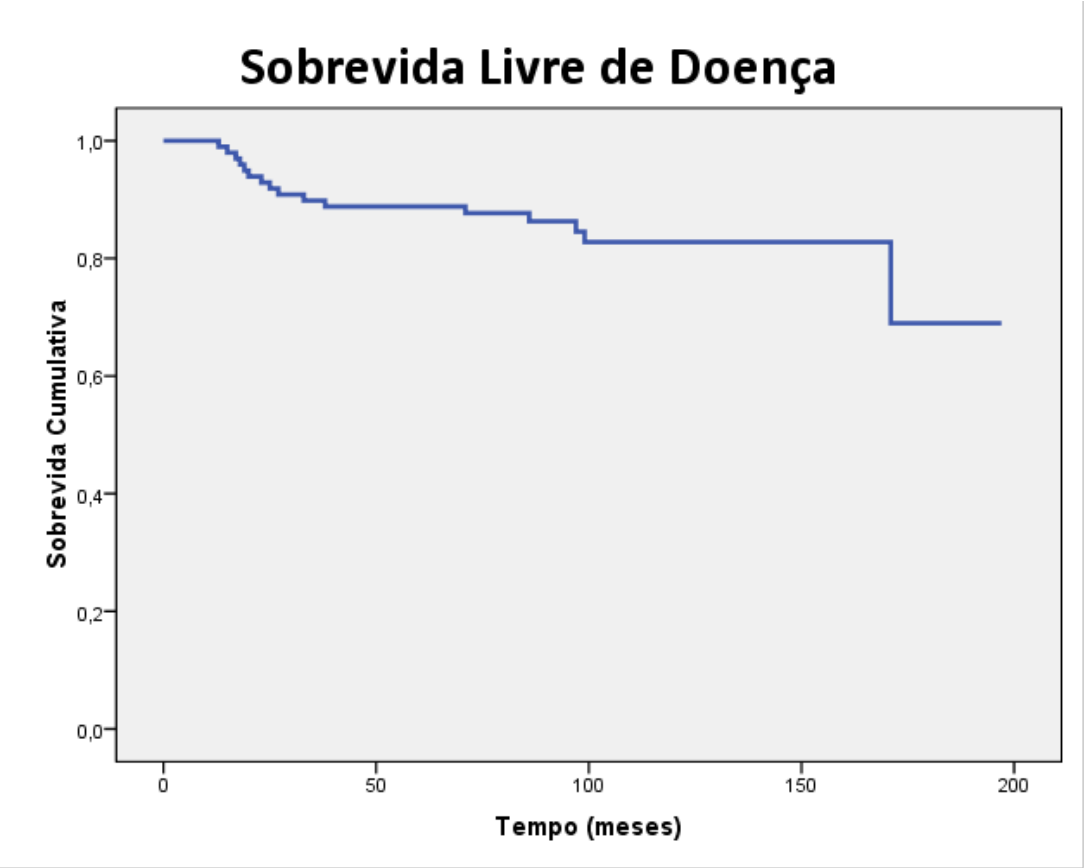

FIG. 3 – MULTIVARIATE ANALYSIS: ANN HARBOR STAGE AS PROGNOSTIC FACTOR

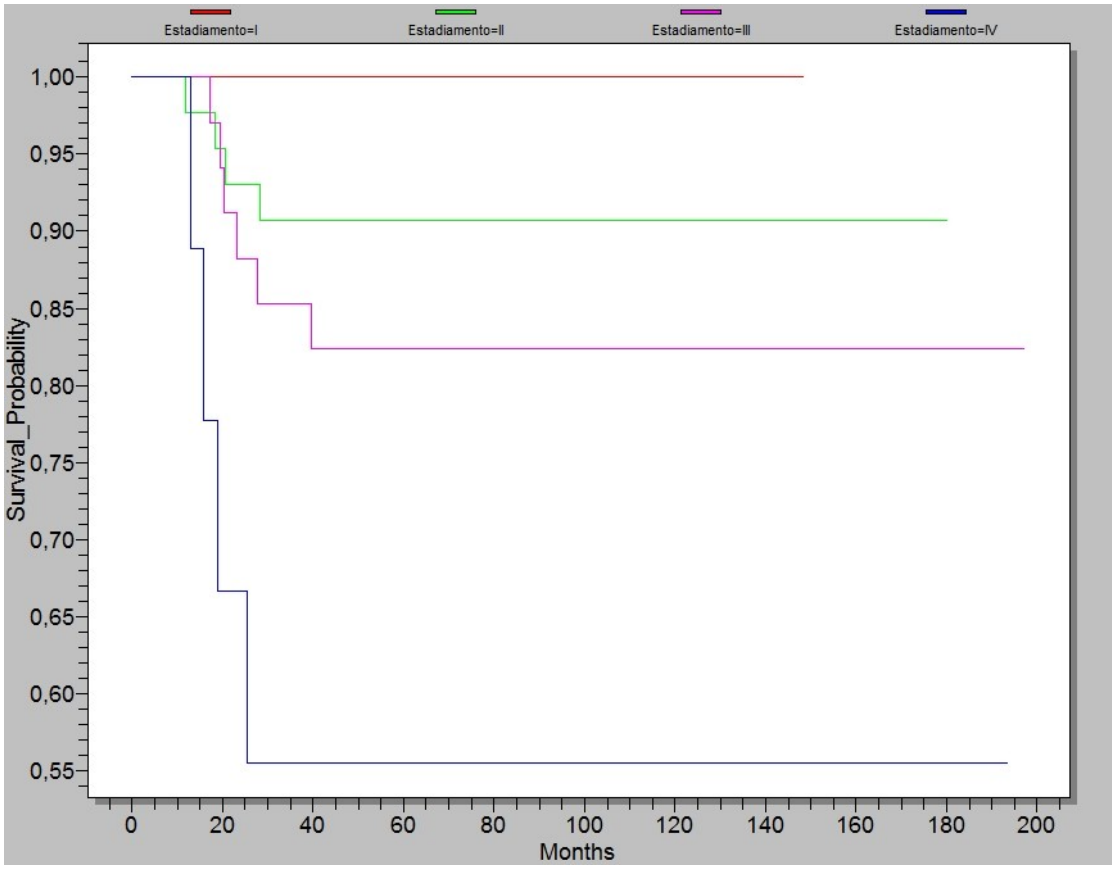

FIG. 4 – NUMBER OF INVOLVED SITES

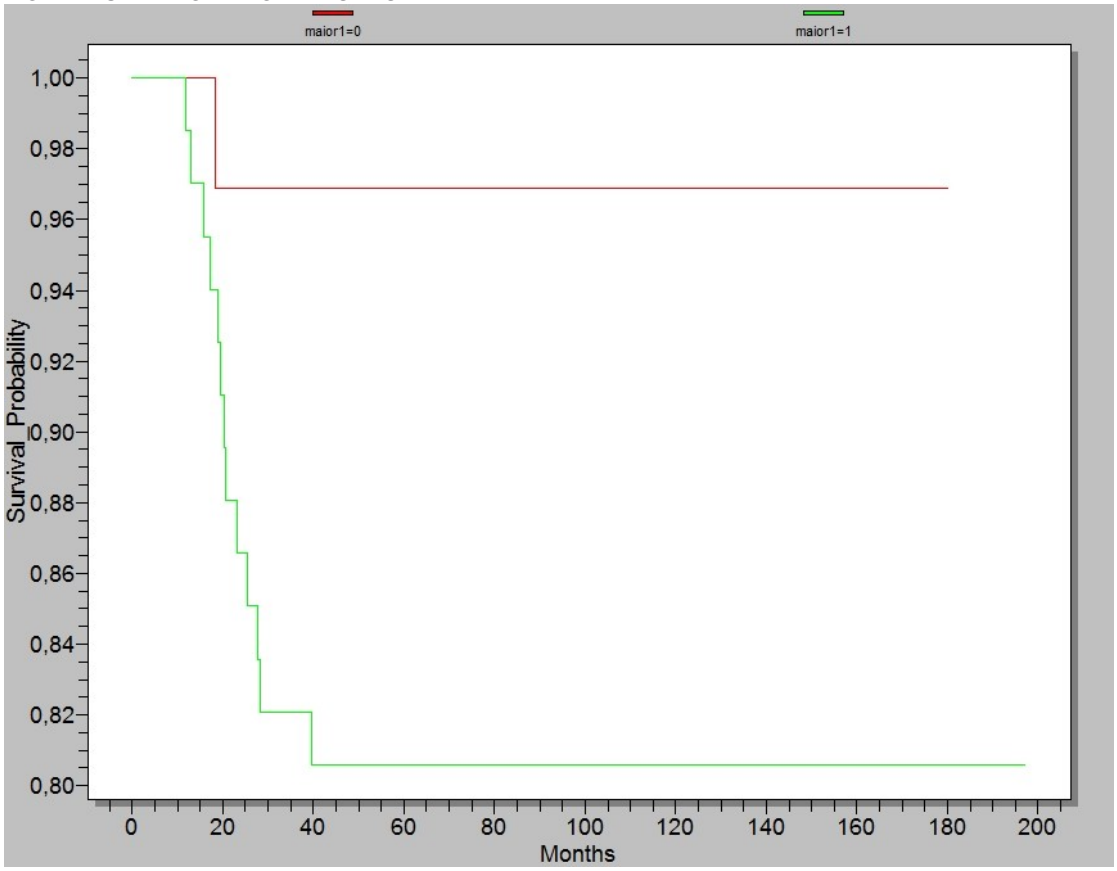

TABLE 1

Table 1. Characteristics of 120 pediatric patients with Hodgkin´s Lymphoma			Krasin et al. n=195	Oguz et al. n=65
Characteristic	No. of patients	%	%	%
Age, years				
≤ 7	33	27.5	-	32.0
> 7	87	72.5	-	67.0
Sex				
Male	84	70.0	58.0	77.0
Female	36	30.0	42.0	23.0
Histologic type				
Mixed cellularity	47	39.1	18.0	38.0
Nodular sclerosis	42	35.0	70.8	37.0
Lymphocyte predominant	20	16.6	9.2	20.0
Lymphocyte depletion	5	4.1	-	5.0
Not specified	6	5.0	2.0	0.0
Ann Arbor stage				
I	16	13.3	18.0	12.0
II	52	43.3	44.6	43.0
III	38	31.6	18.0	35.0
IV	14	11.6	19.4	10.0
Systemic “B” symptoms				
Present	56	46.6	29.7	40.0
Absent	64	53.3	70.3	60.0
Envolved sites at diagnosis				
1	38	31.7	-	-
>1	82	68.3	-	-
Extranodal disease				
Yes	58	48.3	20.5	66.0
No	62	51.6	79.5	34.0
Any bulky disease				
Yes	47	39.1	48.7	26.0
No	73	60.8	51.3	74.0
Bulky mediastinal disease				
Yes	20	16.6	31.3	12.0
No	100	83.3	68.7	88.0
Chemotherapy				
ABVD	40	33.3	-	-
OPPA	24	20.0	-	-
MOPP	13	10.8	-	-
Other	38	31.6	-	-
No	5	4.1	-	-
Radiotherapy				
Envolved field	30	25.0	-	-
Enlarged field	74	61.6	-	-
No	16	13.3	-	-
Hemoglobin (g/dL)				
<11	65	54.1	-	40.0
≥11	54	45.0	-	60.0
Not specified	1	0.83	-	0.0
Specialist sending delay				
<12 months	91	72.4	-	-
≥12 months	29	27.6	-	-

TABLE 2

Table 2. Incidence of treatment failure in 99 patients with Hodgkin Lymphoma[1]

Characteristic	No. of patients	%	EFS 5a	p
Age, years				
≤ 7	21	21%	19	0,52
> 7	78	79%	66	
Sex				
Male	69	70%	59	0,84
Female	30	30%	26	
Histologic type				
Nodular sclerosing	28	28%	22	
Mixed cellularity	43	43%	38	0,59
Lymphocyte predominant	18	18%	17	
Lymphocyte depletion	4	4%	3	
Ann Arbor stage				
I	13	13%	13	
II	43	43%	39	<0,01*
III	34	34%	28	
IV	9	9%	5	
Systemic “B” symptoms				
Present	46	46%	37	0,14
Absent	53	54%	48	
Envolved sites at diagnosis				
1	32	32%	31	<0,05*
>1	67	68%	54	
Extranodal disease				
Yes	46	46%	39	0,77
No	53	54%	46	
Any bulky disease				
Yes	41	41%	36	0,58
No	58	59%	49	
Bulky mediastinal disease				
Yes	16	16%	13	0,53
No	83	84%	72	
Hemoglobin (g/dL)				
<11	42	42%	33	0,07
≥11	57	58%	52	
Specialist sending delay				
<12 months	86	87%	76	<0,05*
≥12 months	13	13%	9	

[1]For prognostic factors analysis, 21 patients were excluded because their treatment finished less than 5 years ago.